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REPORT NUMBER 808

THE EFFECT OF COMMON THERAPEUTIC DRUGS ON VISION

by

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Bureau of Medicine and Surgery, Navy Department
Research Work Unit M4305.08-3001.1i

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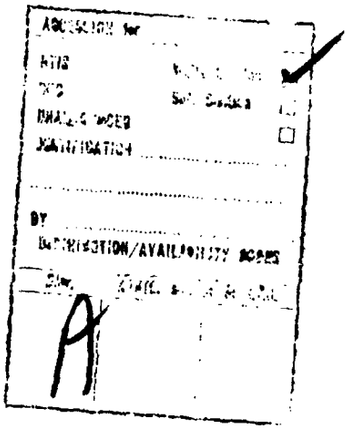

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SUMMARY PAGE

THE PROBLEM

To measure the effects on vision of one therapeutic dose of various widely used drugs.

FINDINGS

One dose of each of several drugs was enough to produce some significant changes of basic visual processes.

APPLICATION

It should be realized that personnel being administered therapeutic drugs are likely to undergo changes in their visual processes, a circumstance which may affect their performance.

ADMINISTRATIVE INFORMATION

This investigation was conducted as part of Bureau of Medicine and Surgery Research Unit M4305.08-3001. The present report is Number 11 on this work unit. It was submitted for review on 11 March 1975, approved for publication on 1 May 1975 and designated as NavSubMedRschLab Report No. 808.

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ABSTRACT

One therapeutic dose of five widely used medicinal drugs (Aralen, Benadryl, Dexedrine, Digoxin and Valium) was administered to 36 subjects. Measurements were made of the effects of the drugs on pupil size, intraocular pressure and the fundus, various aspects of color vision, the electrical activity of the brain, eye-movements and stereoacuity. A number of significant changes were observed despite the small size of the dosage and the number of subjects. The practical implications of the findings are discussed, as well as the value of visual psychophysical tests of pharmacological intoxication. In general, there were more decrements than improvements.

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THE EFFECT OF COMMON THERAPEUTIC DRUGS ON VISION

INTRODUCTION

Current Use of Drugs

"American physicians are currently writing some 260 million psychoactive-drug prescriptions a year" (Brecher, 1972, p. 489). Minor tranquilizers account for around 40 percent, hypnotics for about 18 percent, stimulants for 13 percent, and sedatives and antidepressants for about 10 percent each. Tranquilizers are the most popular drug for patients above the age of 30; amphetamines are the most popular among the younger age groups.

Polling studies indicate that 35 percent of adult Americans – 35-40 million people – used some phychotropic drug in 1967. When respondents were asked if they had ever used such drugs, the answers suggested that around 70 percent of the adult population had done so at some time. Drug usage appears to be the rule rather than the exception in this country.

Moreover, it should be emphasized that "69 percent of all psychoactive prescription drugs secured by males under 30 were secured without a prescription!" (Brecher, 1972, p. 487), under which condition they are quite inexpensive wholesale. It is clear why Brecher concludes (p. 475) that the current drug scene is of "truly gargantuan dimensions." An idea of the dimensions of the problem can be obtained from the bibliography compiled by the National Institute on Drug Abuse (Glenn and Richards, 1974) and from the fact that government expenditures on drug education in 1972 were nearly 500 million dollars (Goldberg and De Long, 1972). The problem is no less severe in the Armed Forces, as Kolb et al, (1974) have recently pointed out.

Importance of Testing Effects of Drugs

Since many of these drugs are used to alter some aspect of perception or behavior, the question must be raised as to the effect of various drugs on the ability to perform those tasks for which the drug-user is responsible. Such questions are of particular importance to the Navy with its highly complex equipment. There must obviously be some concern about the ability of a man to operate such equipment, if he is under the influence of drugs.

When we speak of a drug problem, what comes to mind is the use of illicit or addictive drugs used for other than medical purposes. It must not be assumed, of course, that most of the drugs being taken are in that category. Nor can it be assumed that therapeutic drugs, legitimately prescribed and properly used, do not also present problems. Most therapeutic drugs have unwanted side-effects, at least under certain conditions (Silverman and Walsh, 1971; Silverman, 1972). Willetts (1969) notes that "The eye must manifest side-effects from a wide variety of drugs used in the treatment of diseases of all systems of the body." Leopold (1968) states that "Undesirable ocular effects... may be produced by almost all categories of systematically

administered drugs..." Meier-Ruge (1969) has stated most emphatically that "We must in general once and for all divert ourselves of the idea that we can achieve pharmacotherapy free of all undesired effects" (p. 566).

It is clearly important to know if such side-effects are likely to interfere with the drug-user's ability to perform certain tasks. Yet, the question may arise as to the need for such a study. It is well known that the literature on drugs and their effects is immense. The reader may assume that there is already ample evidence on these questions. However, Uhr (1960) has pointed out that "Thousands of papers about psychoactive drugs have been published in the last few years, but scarcely a hundred have reported objective behavioral tests and their effects on human subjects." Furthermore, the interpretations of drug studies are complicated not only by variations in dosage, chronic or acute administration, different populations, and differences in the state of vigilance at the time of recording (Fink, 1969), but by situational factors (Starkweather, 1959) and personality factors as well (Kornetsky et al, 1957; Claridge, 1970; Claridge and Herrington, 1960).

Reasons for Studying Vision

The present study tested the effects of common therapeutic drugs on various visual processes. There are several reasons for studying the effects of drugs on vision. The first is that it is highly likely that many drugs will have an effect. There is evidence for cholinergic transmission in the retina (Nichols and Koelle, 1968) and it is known that acethycholine increases the spontaneous activity of the ganglion cells, among other effects (Straschill, 1968; Ames and Pollen, 1969). Whether drugs are cholinergic or adrenergic, they are likely to have effects on the visual system (Tredici and Epstein, 1972). Further, as noted above, most drugs are likely to produce side-effects on vision. Since vision is, perhaps, our most important sense, it seems likely that any deterioration here will affect the general performance of the individual.

Another reason for testing the effects on vision of human subjects is that drugs are usually tested for general systemic toxicity primarily on animals. Yet an ocular reaction can be produced in one species and not in others. Crews (1966) cites Paget's example of an antimalaria drug which produced irreversible changes in the eyes of guinea pigs, slight effects in rabbits and monkeys, and no effects in rats, mice, and dogs.

A third reason is that, as Crews (1966) again has pointed out, "It has often been observed that the eye acts as a sentinel, being the first part of the body to show toxic effects in many instances." Thus a study of vision may indicate toxicity at smaller dosages than necessary to affect other kinds of tests. Indeed, observation of the eye and testing of such things as the pupillary reflex have long been a basic element in medical examinations. Carr et al, (1966), in their study of chloroquine retinopathy, have pointed out that a psychophysical exam is more sensitive in detecting chloroquine toxicity than the usual ophthalmoscopic techniques. And Church et al, (1962) have

noted that blurred vision is often the earliest symptom of digitalis poisoning.

Although, as discussed in detail below, many effects on vision have been reported, most are observations on patients who have been treated with drugs for some time. This study measured the effects on normal subjects after one therapeutic dose.

THE DRUGS, THEIR APPLICATIONS AND GENERAL EFFECTS ON VISION

The drugs were chosen because they are among the most widely prescribed therapeutic drugs, each representing a different class and used for a different therapeutic purpose. They include chloroquine phosphate (Aralen), diphenhydramine (Benadryl), dextroamphetamine sulfate (Dexedrine), Digoxin, and diazepam (Valium). Table 1 lists the drugs and dosages, their main uses, and duration of action.

Table 1. The drugs tested, dosage administered, and summary of pharmacologic actions

Drug	Dosage (mg)	Main use	Duration (Hr)
Chloroquine-phosphate (Aralen)	500	Malarial suppressive; arthritis	Half-life after single dose is 3 days
Diphenhydramine (Benadryl)	50	Antihistamine	4-6 hours
Dextroamphetamine sulfate (Dexedrine)	5	Stimulant	1-6 hours
Digoxin	0.75	Heart disease	Absorbed within 2-5 hrs. Most excreted in 2 days
Diazepam (Valium)	5	Tranquilizer	Half-life 7-10 hours

1. Aralen was developed as a malarial suppressive and is still widely used for that purpose. However, it was later found to be of value also in the treatment of rheumatoid arthritis and lupus erythematosus and has been suggested for the treatment of infectious mononucleosis (Cawley and Myers, 1962). It is useful in the treatment of photoallergic reactions, and cardiac arrhythmias, as an anticoagulant and to prevent histamine-induced contractions (Rollo, 1970).

Although the treatment of malaria requires only small doses of the drug, generally not reported to result in harmful side-effects (Appleton et al, 1973), large doses must unfortunately be used to treat the latter ailments. These large doses result in serious ocular complications: blurring of vision, difficulty in accommodation, diplopia, loss of central visual acuity, granular pigmentation of the macula, and retinal artery constrictions (Sloan, 1961; Okun et al, 1963; Henkind et al, 1964; Potts, 1965 Carr et al, 1968; Leopold, 1968).

2. Benadryl was one of the first antihistaminic drugs to be discovered. Although there now exist a bewildering variety of such compounds, it remains one of the most effective. Benadryl is a central nervous system (CNS) depressant. Like other antihistamines, it is used to reduce the intensity of allergic

and anaphylactic reactions by blocking the responses of smooth muscle to histamine. It is used, thus, to treat such allergies of the respiratory tract as seasonal hay fever and pre-asthmatic cough, and allergic dermatoses. It is also used to treat parkinsonism and is very widely used to combat motion sickness (Douglas, 1970).

All antihistaminics elicit side effects. The most common is drowsiness. Benadryl is reported to be the most effective sedative among the antihistamines (Goodman and Gilman, 1960, p. 661). Among its adverse side effects on vision are diplopia and blurred vision (Sloan, 1961). The use of the drug is also warned against in cases of narrow angle glaucoma (Douglas, 1970).

3. Dexedrine is a sympathomimetic drug which has powerful CNS stimulant actions, but less peripheral action (i.e., effects on blood vessels to skin and mucosa, salivary glands, etc.) than related drugs. It is used in a variety of conditions, such as the treatment of hangover, narcolepsy, mental disorders, as an adjunct in epilepsy, and to counteract poisoning by CNS depressants. It is widely used to treat obesity by reducing appetite, and very widely used to combat fatigue and increase wakefulness. Innes and Nickerson (1970) note that the drug should be used for the latter purposes only sparingly and with medical advice. The evidence is that in most cases the drug is being used other than sparingly and without medical advice (Brecher, 1972).

Very few effects on vision are reported for Dexedrine in general reviews. None is mentioned by Innes and Nickerson (1970). Willetts (1969) notes that a possible ocular side-effect is dilation of the pupil, but he cites no behavioral concomitants. A few studies suggest changes in color vision (Kravkov, 1941; Kaplan, 1960) and in such mechanisms as accommodation and convergence (Westheimer, 1963).

4. Digoxin is one of a group of drugs related to digitalis which are collectively known as the cardiac glycosides. They are classified as adrenergic blocking agents. Their main property is the ability to increase the force of myocardial contraction, and their main use is to treat congestive heart failure (Moe and Farah, 1970).

Digitalis has been used as a drug for centuries, and a wide variety of effects on vision including blurring and disturbance of color vision have been reported at least since the 18th century. The digitalis group is one of the group of drugs about which a sizeable literature has accumulated detailing these effects. As with Aralen, there are too many reports to permit a complete bibliography, but an introduction to the literature can be obtained from Sloan (1961), Robertson et al (1966a and b), and Leopold (1968). There are some reports of differential effects of the various glycosides (Dubnow and Burchell, 1965). Since Church et al (1962), in one of the better experiments in this field, found no differences in toxicity from different drugs in the group, results from studies dealing with any of these closely related drugs will be considered.

5. Valium is one of the minor tranquilizers and is similar to the barbiturates. It is a CNS depressant whose

main locus of action is the brain stem reticular system. Valium is widely used in the treatment of anxiety and alcoholism, as muscle relaxants, daytime sedatives, and in the treatment of epilepsy (Jarvik, 1970).

It is reported to produce diplopia and blurred vision (as do alcohol and the barbiturates). Instructions to physicians say that the drug is not to be used in patients with narrow angle glaucoma (Barnes, 1971).

METHOD

Subjects

Thirty-six members of the Laboratory staff, most of them enlisted men, volunteered to participate. All but three were men. They were assigned to the drugs randomly. No woman was given Valium. Jaatela et al, (1971) have reported that Valium produces markedly different effects in women than in men in a number of respects.

Statistical significance

Six subjects were randomly assigned to each drug. The experiment was carried out in two phases. Digoxin was included in both phases, making a total sample of 12 for that drug.

It is, of course, difficult to obtain results which are statistically significant when there are only six subjects. One reversal is generally enough to throw the results outside the accepted confidence limits of five percent. In this study, we will, therefore, consider that an effect shown by 5 of the 6 subjects is worth mentioning, although it may not be statistically significant.

General Procedure

The two phases of the experiment were carried out six months apart. In the first phase, three groups of subjects were tested with Benadryl, Digoxin and Valium; in the second phase, three new groups of subjects were tested with Aralen, Dexedrine and Digoxin.

A double-blind procedure was used. Each subject served as his own control and was therefore tested twice. At least three days elapsed between the two sessions. For each drug, half of the subjects were given the drug on the first occasion and the other half first received a placebo which looked like the drug. However, since most of the subjects were hospital personnel, a further attempt was made to maintain the double-blind procedure, for very small incidental factors may have significant effects (Goodfellow, 1946): to keep the subjects from examining the pills, the individual dispensing them usually put the pill into the subject's mouth. Such a procedure of course minimizes the chances that the experimenters will inadvertently influence the results, but on the other hand it may also reduce or distort psychological components associated with the taking of drugs (Claridge, 1970). Some investigators have expressed concern that the double-blind procedure may also be vitiated by clues from drug effects (Baker and Thorpe, 1957; Cole, 1968) and by the fact that subjects often react to the placebos (Jellinek, 1946; Beecher et al, 1953; Gentles and Llewellyn Thomas, 1971; Lasagna, 1955). On the other hand,

subjects often guess incorrectly as to whether they are on the drug or the placebo, as happened several times in this experiment.

All testing was done at the same time in the morning (Platz et al, 1964). The pills were administered at 7:30 AM and testing began around 8:30. The schedule is given in Table II. Usually two subjects were tested on any one morning, one subject about 15 minutes behind the other.

CHOICE OF TESTS

The brief summary given above of the effects on vision reported to result from the five drugs formed one of the bases for our choice of tests. Since pupil size is well known to be an indicator of drug usage under certain circumstances, we made measurements of the pupil. The warning in the case of several drugs against using them in patients who suffered from glaucoma led us to measure intraocular pressure. The large literature on retinopathy led us to photograph the fundus.

Table II. Schedule of Tests

	AM
Administration of drug	7:30
Color vision tests	8:30
First after-image	9:00
Eye-movements	9:10
Stereoacuity	9:20
Second after-image	9:25
Pupil size photographs	9:35
Visual evoked responses	9:40
Benham's top	10:15
Tonometry	10:35
Fundus photographs	10:45

The reports of color vision disturbances led to the inclusion of several different kinds of tests of color vision. We included routine tests of color defects and discrimination of chromatic stimuli as well as cortical evoked responses to chromatic stimuli. We also included several measures of subjective colors - after-images, Benham's top, and color-memory. Lehmann (1959) has concluded that after-images must be considered in the class of neurophysiological after-discharges and related to retino-cortical fatigue and would therefore appear to be a good test for use in assessing drug effects. Malitz and Kanzler (1970) have criticized investigators for deliberately excluding phenomenological experiences, that is, measures which do not combine both perceptual and motor behavior.

The reports of blurred vision or double vision, or loss of acuity suggested a test of acuity. We tested stereoacuity rather than resolution acuity, since there appeared to be no investigations of this important ability. Chisholm (1968) has not found resolution acuity to be a sensitive measure of drug effects.

We included an analysis of eye movements, which seemed likely to be a sensitive indicator, and finally, we also measured the electrical activity of the brain.

The detailed procedures and results for each test are discussed separately, beginning with the physiological meas-

ures, followed by the color vision tests, the evoked potentials, eye-movements and stereoacuity.

PUPIL SIZE

Pupil size has been a popular indicator in pharmacological experiments. The iris is quite sensitive to many drugs. It has long been known, for example, that morphine causes so marked a contraction of the pupil that it is almost never due to any other cause; the morphine user can thus be detected quite easily. More sophisticated tests involving pupil size have been used to detect the use of very small amounts of this narcotic (Way, 1965; Elliott et al, 1968). During anesthesia, the behavior of the pupil is an aid to determining the depth of narcosis (Adler, 1950). Disturbances of the pupil are commonly noted as secondary effects in various stages of narcosis from a wide variety of substances. Dilation of the pupils and the absence of the light-reflex is a common sign in blindness from many types of intoxication (Sorsby, 1958).

Nevertheless, as Loewenfeld (1963) has noted, "In spite of the great popularity which the iris has enjoyed as an indicator in pharmacological experiments, the number of investigations in which pupillary movements were registered accurately is relatively small."

It is difficult to predict what effect a drug will have on the pupil. The iris is controlled by two muscles: the sphincter is the stronger and so the effect of a drug is largely determined by whether it causes this muscle to relax or contract. Since the pupil is innervated by both sympathetic and parasympathetic fibers, drugs affecting both systems will have an effect.

It is generally stated that the sphincter contracts in response to cholinergic stimuli and relaxes in response to adrenergic stimuli (Davson, 1972, Vol. 4, Lowenstein and Loewenfeld, 1952). But the complexity of the problem has increased with the recognition - after a period of some disagreement (Potts, 1965, p. 355) - that there are both alpha and beta adrenergic actions (Davson, 1972, Vol. 4, pp. 391-394). Moreover, recent evidence indicates at least three distinct classes of beta receptors (Triggle, 1972).

Langham et al, (1971) and Langham and Diggs (1974) have carried out studies which reveal that there are complex effects and interactions, sometimes depending on the concentration of the drug. Little wonder that conflicting results have been reported (Weekers et al, 1955) and that it is difficult to predict a drug's action simply from its general classification.

Tredici and Epstein (1972) state that Digoxin constricts the pupil, but Robertson et al (1966b) reported pupil size to be unaffected by the cardiac glycosides. Sprague et al, (1925) long ago noted that both pupillary dilation and constriction have been reported to result from digitalis. Perhaps, as Loewenfeld (1963) has pointed out, such inconsistencies are due also to the great variations in responses among individuals, and even in the same individual under different conditions.

Westheimer (1963) and Campbell et al, (1972) reported no change in pupil

size with amphetamine, but Bradshaw (1970) found an increase in pupil diameter with the same dose. Sigg and Sigg (1973) reported that Valium reduces the light reflex.

In quantifying the effects of drugs on the pupil, it has been common to monitor the pupil diameter under constant illumination and note changes occurring with time. In this study, we have measured the magnitude of the light reflex in response to a low and a high light level.

Method

Pupil diameters were obtained by photographing the subject's right eye under the two conditions of illumination. A millimeter ruler was placed against his cheek directly under the eye, and pupil-diameter was then measured from the photograph (Fig. 1).

The subject sat with his chin on a chin-rest in a room illuminated only by the horizontal beam of a tungsten light. This lamp was mounted at eye-level one meter from the subject, positioned so that it was 45° to the right of the subject's line of sight to the camera.

The dim level of illumination was produced by pointing the light away from the subject, perpendicular to his line of sight. This resulted in a light-level of 0.2 ft-candles measured by a Weston foot-candle meter placed in the plane of the pupil. The bright level of illumination was produced by pointing the light directly at the subject. This resulted in a light-level of 45 ft-c.

Photographs were made first under the dim level of illumination after the subject had adapted to it for two minutes. Lowenstein and Loewenfeld's data (1959) indicate that the pupil is virtually fully dilated within 10 seconds after exposure to dimmer light. Two photographs were taken at each light-level and the measurements for each level averaged. The photographs in the bright condition of course necessitated no additional lighting, but photographs in the dim condition were taken with an electronic flash. There was a ten-second pause between the two pictures, which was considered ample time for the pupil to recover (Lowenstein and Loewenfeld, 1959).

Results

The mean pupil diameters for each group of subjects are given in Table III for both the drug and placebo conditions under both light levels. Table III also

Fig. 1. Sample photographs of the pupil taken under dim (left) and bright illumination

Table III. Mean pupil diameter (mm) in drug and placebo conditions under dim and bright light levels

	Dim Illumination			Bright Illumination			Difference in ranges of response (Drug - Placebo)
	Drug	Placebo	Diff.	Drug	Placebo	Diff.	
Aralen	6.09	6.28	-.19	2.77	3.26	-.49	+.30
Benadryl	5.50	6.14	-.64*	3.29	3.34	-.05	-.59*
Dexedrine	5.64	5.69	-.05	3.34	2.85	+.49	-.54*
Digoxin	6.58	6.08	+.50*	3.27	3.58	-.31	+.81**
Valium	6.39	6.22	+.17	3.91	3.55	+.36	-.19

* Effect occurred for 5 of 6 subjects (11 of 12 for digoxin).

** $p < .03$

gives the differences between these mean values - the mean range of response of the pupil.

In the placebo condition, the mean diameter of the pupils under dim illumination ranged from 5.69 to 6.28 mm in the various groups, a range of 0.59 mm. Under the drugs, the range was 1.08 mm, nearly twice as great. Similarly, under bright illumination, the range was 0.70 mm in the placebo condition and 1.11 mm under the drugs. The drugs evidently had an effect.

The last column of Table III shows the mean change in the response ranges of the pupils under the drugs. Mean pupil diameter under Aralen, for example, was 6.09 mm in dim light and 2.77 mm in bright light, a range of 3.22 mm. Under the placebo, the response range was only 3.02 mm. The drug, thus, increased the response range by 0.20 mm. Among the various range changes the increase was significant for Digoxin (paired $\underline{t} = 2.65$, df = 11, $p < .03$) and a decrease in range occurred for 5 out of 6 subjects under both Benadryl and Dexedrine.

The range of response can vary for three reasons: because the magnitudes of both dilation and constriction are changing, or because only one of them is changing. When the changes in pupil size are analyzed for a given level of illumination, it turns out that Digoxin very reliably increased the magnitude of dilation in dim light ($\underline{t} = 4.09$, $p < .001$). In bright light it also increased the amount of constriction, but this change was not significant ($\underline{t} = 1.74$, $p < .12$).

Benadryl increased the amount of dilation in dim light in five of the six subjects. With Dexedrine, the decrease in response-range was due to less constriction under bright light.

Discussion

Digoxin reliably increased the response-range of the pupil. It significantly increased the magnitude of dilation in dim light and tended to increase the magnitude of constriction in bright light. It is not clear why these results differ from the lack of change reported by Robertson et al, (1966b). Their dosage greatly exceeded ours. They gave their subjects 2.5 mg (more than three times our daily dose) for three days followed by 0.5 mg for 11 days and found no effect on either pupil diameter or latency of pupillary response. In testing digitalis and digitoxin, they also used much higher doses than the present dose without effect. Perhaps the most reasonable explanation is that their subjects had adapted to the drugs by the time of testing.

Our results with Dexedrine conform to those of Bradshaw (1970) who also found an increase in pupil diameter in bright light. Westheimer (1963) found no change. But it should be noted that, quite apart from the general variability in the effects of drugs already mentioned above, a number of studies have shown great variability of effect for amphetamines specifically. For example, Starkweather (1959) has shown a reversal of effects of Dexedrine as a function of situational influences. And Tecce and Cole (1974) have reported that amphetamine produces "paradoxical"

drowsiness in two-thirds of their subjects and the expected alertness in only one-third. Such individual differences may have produced the discrepancies between the different experiments.

INTRAOCULAR PRESSURE

Intraocular pressure (IOP) is of concern when drugs are administered. Just as some drugs are used to reduce pressure, others have the undesirable side effect of raising it. Abnormally high pressure is usually - if not always (Allen and Wertheim, 1966) - indicative of a serious disturbance known as glaucoma. The use of Benadryl and Valium is cautioned against in cases of narrow angle glaucoma presumably because it may further raise IOP, whereas Digoxin, e.g., is thought by some to reduce IOP (Goodman and Gilman, 1960; Potts, 1965).

The effects of many drugs are not certain, however. Intraocular pressure is governed by the rate at which the aqueous humor is secreted into the eye and the resistance that it meets in escaping to the veins on the surface of the eye (Grant, 1969). Cholinergic drugs are generally thought to reduce pressure, whereas anti-cholinergic drugs may increase pressure (Potts, 1965). Yet Hiatt et al, (1970) found no appreciable increase in IOP after systematic administration of an anti-cholinergic drug. Weekers et al, (1955) found that norepinephrine decreased IOP, but Langham et al, (1971) found that it increased IOP.

A number of investigators have reported that Digoxin reduces IOP (Simon and Bonting, 1962; Desvignes et al, 1963; Smith and Mickatavage, 1963; Hegazy et al, 1967) but Peczon (1964) and Pilz (1967) reported that it does not.

Valium is reported to produce a significant reduction when injected intravenously (Ferreira et al, 1969; Rosignoli, 1970). But with oral administration, there is said to be only a slight initial reduction with no lasting effects (Grant, 1968).

Conflicting results have also been reported for Dexedrine, leading Grant (1969) to comment that there has not been enough attention paid to spontaneous diurnal variations of IOP. We are not familiar with any investigations dealing with the effects of Aralen and Benadryl on IOP.

Many of these studies were carried out on patients suffering from glaucoma and using intravenous injections. Even if a change in pressure was obtained with such people, similar effects might well not be found in normal subjects with oral administration (Hegazy et al, 1967). For this reason, we have included IOP as one of the measurements in our test battery.

Method

Intraocular pressure was measured with a Schiotz tonometer after instillation of two drops of 0.5 Ophthetic in the subject's right eye.

Results

Table IV presents the mean IOPs for each drug and its placebo. The normal range of IOP is from 14.6 to 20.6 mm Hg.

Table IV. Mean intraocular pressure (mm Hg) under drug and placebo conditions

	Drug	Placebo
Aralen	17.4	17.0
Benadryl	16.7	16.7
Dexedrine	18.0	17.7
Digoxin	18.7	17.8
Valium	16.3	17.0

There were virtually no changes in mean IOP as a result of the drugs. No changes were statistically significant. Indeed, there were no trends. For every drug the changes appeared to be random. In no instance did the IOP fall outside the normal range.

Discussion

There was no evidence in this study that one therapeutic dose of any of these drugs produced a change in IOP. The question arises as to the reasons for the negative findings when many previous studies have reported changes for three of the drugs in question. The answer appears to be, first, that most of the previous studies involving these drugs have been performed on patients suffering from high IOP. There is little data on the effects on normal subjects. Hegazy et al, (1967) did have a control group of normal subjects. They reported that Digoxin lowered the mean IOP from 18.47 to 16.71 mm Hg by the fifth day. But these values are well within the normal range, of course. Moreover, Hegazy et al noted that on the sixth day IOP rose, although the administration of the drug had not been terminated. Obviously the decrease in IOP was quite small even after a week. Certainly, it did not compare with the drop in IOP for glaucomatous patients, whose mean IOP was lowered from 35.22 to 26.16 mm, a drop of 25%.

Second, in many of the previous studies the drugs were not administered orally. Smith and Mickatavage (1963) used a topical application directly on the cornea. Pilz (1967) found that intravenous injections of Digoxin were effective in lowering IOP, but neither oral administration of .1 mg digitoxin nor local application of 6.25 to 12.5 mg of Digoxin per 100 ml of a solvent had any effect. Desvignes et al, (1963) reported variable results with 0.25 mg a day administered orally and noted that they had abandoned oral administration of Digoxin. And Peczon (1964) found that .25 mg of Digoxin administered orally two to four times a day over a period of two weeks had little effect on IOP. Simon and Bonting (1962), in their path-finding study, found a decrease in IOP after administering Digoxin orally. But their baseline was extremely variable, and the extent of the reduction is not completely clear.

Both Ferreira et al, (1969) and Rosignoli (1970) reported that intravenous injections of Valium reduced IOP. The correlation between the dose and the change in IOP reported by Rosignoli was quite variable, although there is a clear regression line. When our dose of 5 mg is converted to mg/kg of body weight (assumed mean body weight of 150 lbs.), then our dose turns out to be below the mean level of his dosage.

Eight of his subjects received roughly the same dose as our subjects. Intravenous injection of Valium reduced their IOP from a mean value of 14.48 to 11.55 mm. Both mean values are below the normal range. Interestingly, Rosignoli states that one of these subjects was glaucomatous but his IOP is given as 18.86 which is within the normal range.

Ferreira et al reported a drop in IOP from 12.11 to 9.50 mm after intravenous injection of Valium. The drop of 2.6 mm is not very great. Again, both of their mean IOPs are below the normal range.

In summary, a review of previous investigations would not lead us to expect any of the drugs in this study to produce much of a drop in IOP. Reductions have been found essentially only for intravenous injection of patients with abnormally high intraocular pressures to begin with.

RETINOPATHY

It is well known that certain drugs result in damage to the eye. The most widely studied are the various drugs in the chloroquine (Aralen) family: there is a large literature devoted to their deleterious effects on the retina, cornea, and visual perception (Okun et al, 1963; Henkind et al, 1964; Scherbel et al, 1965; Meier-Ruge, 1969; Gregory et al, 1970; Ramsey and Fine, 1972). Digitalis has an affinity for the optic nerve and can cause retrobulbar neuritis (Wagener et al 1946). The earliest ophthalmic signs of chloroquine toxicity are mottling of the macular or a ring of pigment distribution about the macular which may develop into optic atrophy and attenuation of the arteries (Duke-Elder, 1954).

There has been some question, however, as to what magnitude of dose is required to produce observable retinal changes. The evidence now seems to indicate that retinopathy results only in those individuals who have been treated with more than 250 mg/day for prolonged periods. As Henkind et al, (1964) point out, "In small dosage there has been little or no evidence of damage". . . On the other hand, "with prolonged use. . . .there is a high incidence of ocular side effects." Scherbel et al, (1965) concluded after a study of over 400 patients that with the usual low dosage of 200 mg/day there is no evidence of abnormalities with the usual ophthalmic techniques. We would thus not expect to see any changes in the retina after one dose, even if there were psychophysical changes. The latter produce evidence of chloroquine toxicity before damage to the eye can be seen with an ophthalmoscope (Carr et al, 1966; 1968).

A second group of drugs which has also been rather widely studied for its effects on vision and the visual apparatus is the digitalis family which has been reported to produce retrobulbar neuritis (Wagener et al, 1946; Sykowski, 1949). Leopold (1968) notes that patients receiving digitalis therapy should be examined for the presence of scotomata. It has also been pointed out that "at times digitalis intoxication may develop on small doses of the drug. . . in patients who have previously been treated with digitalis. . ." (Sodeman,

1965). Leopold (1968) states that "the interval between the initially orally administered dose and the first manifest symptom of toxicity may be as short as one day." However, Duke-Elder (1954) states that these are only isolated reports; there is usually almost no evidence of organic defect despite any subjective complaints of disturbed vision.

There have been only a few studies of the effect of Valium on the retina, or indeed, on any aspect of vision, and we are not aware of any studies of the effects of Benadryl and Dexedrine.

Method

Four photographs were taken with a Zeiss fundus camera after the subject's right eye was dilated with Mydriacyl (.005). Three photographs were of the fundus; the fourth was of the red reflex. All were examined for any evidence of abnormality in appearance. In addition, the photographs were studied with a 10X measuring microscope, manufactured by Central Scientific Co., capable of measuring to .01 mm. The diameters of the arteries and veins were measured according to the techniques developed by Kinney et al, (1970) and the ratios of artery to vein calculated.

Results

There were no changes in the appearance of the retinas and no sign of any deleterious effect. Table V gives the mean diameters of the arteries and veins for each drug and its placebo condition, as well as the artery/vein ratios. There are no apparent differences between the two sets of ratios and all are in the normal range.

Table V. Mean diameters of arteries and veins (micra) and artery/vein ratios

	Drug Condition			Placebo Condition		
	Artery	Vein	A/V Ratio	Artery	Vein	A/V Ratio
Aralen	112	152	.74	104	140	.74
Benadryl	104	140	.74	112	140	.80
Dexedrine	108	152	.71	111	156	.72
Digoxin	112	144	.78	112	148	.76
Valium	104	136	.76	112	144	.78

COLOR DISCRIMINATION

Alterations in the color sense are frequently reported as effects of drugs (Lyle, 1974). These changes can be broken down into two categories. The first involves the perception of colors as more highly saturated or somehow enhanced as well as reports of colored hallucinations. These, of course, are usually the result of the psychotomimetic drugs (e.g. Hartman and Hollister, 1963) and their cause is not yet fully understood. The second set concerns the deterioration of color discrimination and often reflects the results of damage to the visual system, usually as the result of prolonged use of a drug.

Restricting our review primarily to the drugs used in this study, the largest number of reports have apparently been concerned with the effects on color vision of the digitalis group and of chloroquine (Aralen).

Digitalis has been used as a drug for centuries. Some of its effects on vision were reported in the eighteenth century

(Withering, 1785, cited by Robertson et al, 1966a), when it was noted that the drug produced a general blurring of vision as well as a green or yellowish cast covering the visual field. These observations have been made repeatedly since then, with the additional observations that sometimes objects appear blue; or often they appear to be covered with frost or snow (Sprague et al, 1925; Langdon and Mulberger, 1945; Wagener et al, 1946); sometimes bright sparks or spots of colored light are seen (Frandsen, 1957); and that the visual disturbances may be worse in bright light (Gillette, 1946).

It appears that such visual disturbances occur only after a critical amount of the drug has been ingested. Robertson et al, (1966a) reported on the vision of three patients who had been taking around 0.2 mg/day of digitalis for extended periods. One had blue chromatopsia. The other two had various visual disorders, but no color vision disturbances. They subsequently carried out an experiment in which they administered varying amounts of either digitalis, digitoxin, or digoxin to three (presumably normal) subjects for several days (Robertson et al, 1966b). They found no effects on either the H-R-R plates or the 100-Hue test.

On the other hand, Grutzner (1969) examined a patient who exhibited symptoms of Digoxin intoxication after six weeks of therapy and reported that the D-15 panel showed an advanced tritan defect. The hue-discrimination curve showed a loss of sensitivity in the short wavelengths. Babel and Stangos (1972) also reported that Digoxin poisoning produced a tritan response axis on the 100-Hue test.*

To further complicate the picture, there are the results of the study by Gibson et al, (1965). These investigators have carried out the most careful analysis of the color discrimination of an individual suffering from digitalis toxicity. The man had accidentally been given three times the routine daily maintenance dose, for three weeks (0.4 mg/day) and began complaining of the familiar visual disturbances. Gibson et al, administered the H-R-R plates, the 100-Hue test, the Nagel anomaloscope, and determined his luminosity curve. The latter showed a loss in the red wavelengths and increased sensitivity to the blues. The other tests all indicated the presence of a red-green defect, protanomaly.

A sizeable number of reports have been concerned with the effects of Aralen, because of its retinopathic properties have been well documented since the war.

Okun et al, (1963) reported on the color vision of eight patients who had had a total of at least 200 g of the drug. They could not identify the H-R-R plates and several could not pass the Farnsworth D-15 panel. The defect was reported as being tritanopic in character.

Henkind et al, (1964) found no evidence of color vision abnormalities on the Ishihara H-R-R plates, or the D-15

* *Appelmans (see Babel and Stangos, 1972, p.566) noted that Babel and Stangos did not specify exactly which digitalis compound had been used. However, Church et al, (1962) found no differences in effects between four glycoside preparations.*

panel in 39 patients who had been treated with at least 250 mg/day for a period of 1 to 7 years.

Carr et al, (1966) tested 14 patients who had been on Aralen therapy for prolonged periods with the H-R-R plates and the D-15 panel and obtained normal results from all but one; that patient missed the first two H-R-R plates. He had had a total dosage of 163 g over a 47-week period, a dosage roughly equal to the median dosage for the group.

In the wake of such conflicting data, Crews (1966) concluded, after a survey of 60 patients on prolonged Aralen therapy, that deficiencies on the H-R-R and Ishihara plates occur only after evidence of retinopathy has developed. However, Lakowski and Davenport (1968) pointed out that previous studies which had failed to find color vision defects generally used tests of color-confusions designed to screen out color-defectives. They believed that more sensitive tests, such as the anomaloscope and the 100-Hue test, are necessary to detect small color vision losses. In their study of 27 patients who had been given "small" doses of Aralen for only a "short" period of time, they found that the error-scores on the 100-Hue test gave a plot resembling that of normal subjects who were, however, much older.

Grutzner (1969) next pointed out that patients with Aralen retinopathy arrange the D-15 panel (but not the 100-Hue test) in a way characteristics of a tritan. He therefore raised the question, why should they fail H-R-R plates which were constructed for deuteranopes and protanopes? Grutzner measured the hue-discrimination curves of such patients and concluded that the reason was a general loss of ability to discriminate hues throughout the spectrum. He also concluded as Crews did, that there were no color defects in those patients who were free of scotomas.

Laroche and Laroche (1972) tested the effects of a therapeutic dose of Aralen (and 55 other drugs) on the 100-Hue test. They did not specify the exact dosage of the drugs and did not give detailed results of all their tests. But they reported that Aralen was among those drugs that produced a slight decrease in color discrimination, primarily in Panel 1 (yellows and orange). Indeed, they concluded that the presence of a chlorine atom is particularly harmful for color vision.

Larcohe and Laroche (1972) also appear to have conducted the only study of the effects of Valium on color vision. They noted that a therapeutic dose of Valium was among a group of drugs which produced a relatively large decrement in color vision, as measured with the 100-Hue test. No experimental details are given, and we do not know either the exact dosage or the specific errors.

We know of no studies dealing with the effects on color vision of Dexedrine or Benadryl. However, Dexedrine is a sympathomimetic drug and two reports may be noted in this connection. Kravkov (1941) investigated the effects on color vision thresholds of unspecified sympathomimetic and para-sympathomimetic substances. He reported that the former increased sensitivity to green and the latter decreased sensi-

tivity to it. Kaplan (1960) investigated the effects of ephedrine sulfate (a sympathomimetic) and neostigmine bromide (a parasympathomimetic) on the brightness level needed to extinguish an afterimage. Kaplan concluded that the sympathomimetic drug sensitized observers to red. These two sets of results do not appear to conform, although it must be said of course that the procedures are quite different.

The fact that certain drugs may produce changes in color perception is of intrinsic interest. Such changes in color vision have practical implications for the performance of work which requires color discrimination, of course. Moreover, such findings have also been used to deduce the locus of a drug's action. It is widely accepted that in acquired color vision defects, red-green discriminations suffer when the optic nerve or ganglion layer of the retina is affected, and blue discriminations suffer when the photoreceptors are affected (François and Verriest, 1961; Kelecom, 1963; Kalmus, 1965; Grutzner, 1972; Verriest, 1972), although opinion on this point is not unanimous (Gibson et al, 1965).

Finally, several investigators have pointed out that sensitive tests of color vision are better indicators of disturbances in the visual system than other measures, such as visual acuity, and are, therefore, good indicators of low levels of toxicity and incipient disability (Bronte-Stewart, 1968; Chisholm, 1968; Foulds, 1968).

The Tests

A battery of tests is desirable in testing for color vision alterations (Paulson, 1974). We have included the following tests:

The Farnsworth-Munsell 100-Hue test (Farnsworth, 1943) is one of the most widely used tests of color discrimination (Hsia and Graham, 1965). Lakowski and Davenport (1968) have concluded that it is perhaps the most sensitive and useful instrument for testing for small changes in discrimination. Verriest et al, (1962) and Dubois Poulsen (1972) state that it is the most important test for acquired dyschromatopsias.

The test consists simply of about 100 color-samples which encompass the entire spectrum. The colors are divided into four sets. Each set has two end-points. The subject's task is to arrange the colors into an orderly series from one end-point to the other. In scoring the tests, account is taken both of the number and the pattern of mistakes. In addition, a record is kept of the time taken to complete each arrangement.

The Hecht-Shlaer Anomaloscope is one of the most sensitive of the standard tests of color vision defects (Willis and Farnsworth, 1952). It is designed to measure the so-called Rayleigh-equation - that mixture of red and green light which matches a standard yellow light. Both the mean and the range of

match-points were determined. These color matches accurately differentiate between individuals with normal color vision and the two groups of individuals called protans and deutans who exhibit defects in red-green discriminations.

Pseudo-Isochromatic Plates are standard screening devices for quickly identifying the more serious color defectives. We used a selection of plates published by the American Optical Company for screening out protans and deutans, as well as the plate devised by Farnsworth (see Wright, 1952) for tritans.

Color Memory was tested by presenting the subject with sets of Munsell chips and instructing him to pick out the chip which best matched various familiar objects whose natural colors ranged through the spectrum. Battersby (1973) had studied such tests and concluded that the trained eye, at least, can become so familiar with a color that "there is developed an 'inward eye', a colour memory against which physical samples can be compared with considerable accuracy." Seven sets were used, composed of 3 to 6 chips which were of the same chroma and brightness, but varied in saturation. Matches were made to a "purple plum," "blue sky," a "lime," a "green olive," "yellow mustard," a "ripe tomato," and a "Maraschino cherry." The seven sets of chips are plotted on the C.I.E. diagram in Fig. 2

Results

Farnsworth-Munsell 100-Hue

The mean scores on the F-M 100-Hue test are given in Table VI for each drug and its placebo condition. (Three of the 36 subjects were found to be color defective and were excluded from these analyses.) Two were in the Digoxin group and one was in the Valium group. None of the changes was significant although the decrease with Dexedrine approached significance ($p < .10$). Four of the 6 subjects were worse with the drug and one stayed the same.

Table VI. Mean error-scores on the F-M 100-Hue test (color defectives excluded)

	Drug	Placebo
Aralen	26.7	29.3
Benadryl	33.3	40.0
Dexedrine*	32.7	21.3
Digoxin	39.2	36.7
Valium	27.2	20.8

* $p < .10$

Table VII gives the mean times taken by the subjects to complete the test. There was a significant reduction in time for Dexedrine ($p < .02$). No other change was statistically significant.

In evaluating the changes in the error scores, it is worthwhile analyzing the errors according to their spectral location, in case the drugs affect discrimination in only certain parts of the spectrum as noted above.

Figure 3 (a-e) shows the mean differences in errors made with each individual color-chip in the 100-Hue

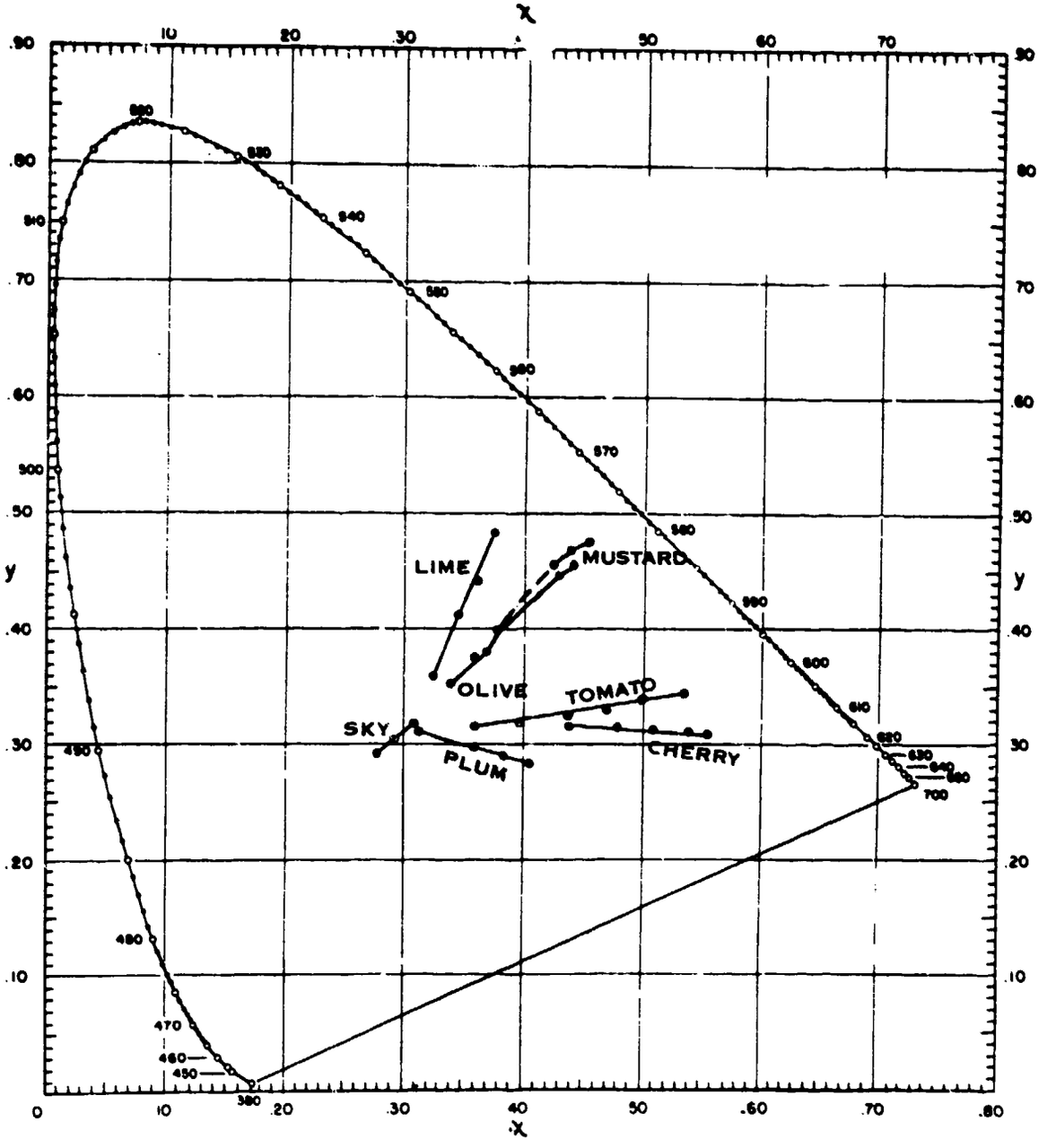

Fig. 2. C.I.E. coordinates of the Munsell color samples used to test color-memory for seven common objects

Table VII. Mean times (sec) to complete the F-M 100-Hue test

	Drug	Placebo
Aralen	386	400
Benadryl	406	390
Dexedrine*	422	498
Digoxin	472	456
Valium	524	544

* $p < .02$

series under each drug compared to its placebo condition. For Aralen (Fig. 3a), the increased errors are most prevalent around 480-510 nm and 580-590 nm. In the purples and between 520 and 580 nm, there is more improvement than degradation under the drug. Only one of the six subjects showed fewer errors in the third panel (495-470 nm).

No other changes approached statistical significance. However, there was, on the average, improvement on every

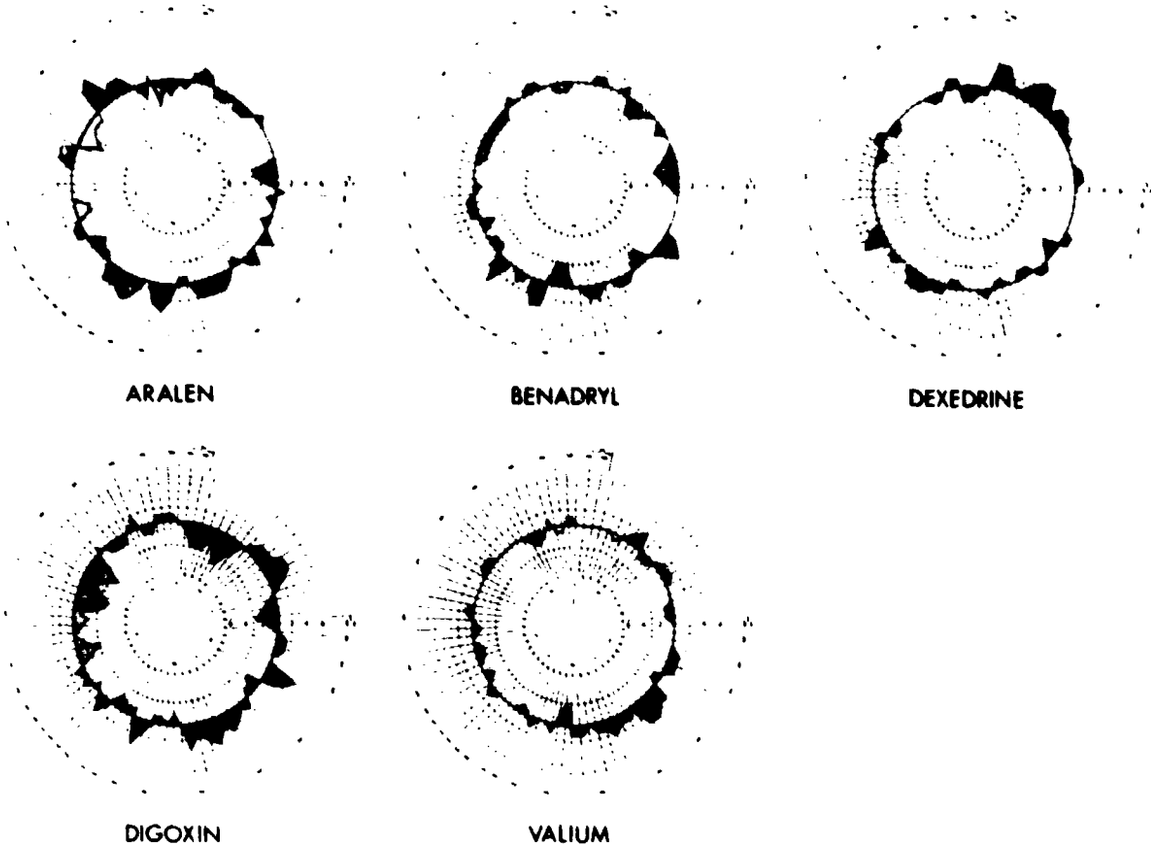

Fig. 3. Mean difference in errors on the Farnsworth-Munsell 100-Hue test as a result of the various drugs. Solid areas indicate an increase in the number of errors; hatched areas indicate a decrease in errors.

panel with Benadryl, although there is no pattern to the changes in the error-scores. It may be noted that 5/6 subjects took longer to complete the test under Benadryl.

With Dexedrine, there was a heavy concentration of increased errors in the purples and greens. Every subject made more errors on Panel 4 (purples) under the drug. Here there appears to be an axis to the pattern, but it does not correspond to one of the familiar dichromatic axes.

With Digoxin, the increases in errors are in the short wavelengths, and most of the improvements are in the long wavelengths. Again, there is no discernible axis to the pattern of changes.

There were very few changes under Valium, most of the additional errors were in the blues.

Hecht-Shlaer Anomaloscope

All responses on the anomaloscope were within normal limits except for the three color defectives. Indeed none of the drugs produced the same effects in 5/6 subjects. None of the changes under the drugs was statistically significant.

Pseudo-Isochromatic Plates

There were no changes in the responses to the plates.

Color Memory

Table VIII gives the frequencies with which different color chips were chosen as a match to the set of objects under the various drugs compared to that in the placebo condition. Since each subject was asked to make 7 matches, there should be a total of 42 judgments for each drug except for the double group under digoxin. (The totals do not always equal these figures because a subject occasionally reported that he could not make a match.)

Table VIII shows that the subjects generally chose the same color chip under both conditions. This occurred on 65% of the judgments. When a different chip was chosen, the direction of the changes was rather evenly divided between the more and less saturated chips for Digoxin and Valium. However, under Aralen, 11 of the 13 changes were of more saturated chi . This would occur if the color samples appeared to the subject to be less saturated than under the placebo condition. Under Benadryl, on the other hand, 10 of the 13 changes were of less saturated chips. Dexedrine also produced a preponderance of more saturated matches, but there were only 8 instances of different chips being chosen under the drug.

Table VIII. Total frequency with which a more or less saturated color-chip was chosen in the drug conditions as a match to seven common objects (Matches to three objects in parentheses)

	More	Less	Same
Aralen	11 (3)	2 (1)	29 (14)
Benadryl	3 (2)	10 (6)	24 (10)
Dexedrine	6 (4)	2 (0)	34 (14)
Digoxin	13 (7)	16 (9)	53 (20)
Valium	9 (5)	7 (1)	25 (12)

Another analysis was made of the matches made using only the three sets of chips which contained 5 or 6 choices (mustard, tomato, and cherry). The assumption was that for these sets it would be more difficult to remember which chip had been chosen in the first condition. The results are given in parentheses in Table VIII. Once again 65% of the judgments were unchanged in the drug condition. The margin of more saturated choices was diminished for Aralen, but increased for Valium. The others are essentially unchanged.

Discussion

The changes in color discrimination resulting from the drugs are very small, which is not surprising in view of the small doses. Most of the previous reports have found alterations in color discrimination only after prolonged use of drugs. Okun et al, (1963) concluded that a total of about 200 g or more of Aralen was needed to produce failure on the Farnsworth D-15 panel. Crews (1966) concluded that deficiencies in color discrimination occurred only after retinal lesions had developed. In the light of such statements, it is surprising that any changes occurred in this study. Yet, although small, there were certain reasonable trends and interesting consistencies.

The most marked effect was the highly reliable decrease in the time taken to complete the 100-Hue test under Dexedrine. But since one of the main uses of the drug is to increase wakefulness, combat fatigue, and produce an energetic feeling, this too is hardly surprising. What is interesting in this connection is the increase in errors, a trend which was almost statistically reliable. This accords well with the effects on psychological processes reported for Dexedrine. Goodman and Gilman (1960), for example, state that "amphetamine results in increased wakefulness, alertness, initiative, motor and speech activity, but it does not improve performance. The initiative rather than ability to do mental work is increased" (p. 518). They go on to say that "It is generally agreed that the diminished sense of fatigue is purely subjective... amphetamine does not enable subjects doing rapidly exhausting work to perform longer or recover more quickly." Color matching is not exhausting work, of course, but the increased speed is not accompanied by increased accuracy of discrimination.

Among the color changes, only Benadryl produced a reduction in the mean number of errors on every panel in the 100-Hue test. It was also the drug under which the greatest proportion of less saturated color chips was chosen on the color memory test. (The selection of less saturated chips suggests a greater sensitivity to the stimulus colors.)

Dexedrine was the only drug in this study which produced an increase in the number of errors in the reds and greens on the 100-Hue test. This does not conform with the results of either Kravkov (1941) or Kaplan (1960). Kravkov reported that a sympathomimetic drug increased sensitivity to green and Kaplan reported that it sensitized observers to red. In any event, we tend to ascribe the increase in errors under Dexedrine not to any sympathomimetic

effects on the color vision system, but rather to the increased speed of taking the test under that drug.

THE FLIGHT OF COLORS

The changes in the perception of colors commonly reported by users of a variety of drugs range from an increase in the brightness and saturation of objective colors to the experience of chromatic hallucinations. Such changes do not appear to have been quantified, however; we have only qualitative statements and introspective reports.

There is some evidence that these phenomena have a physiological basis. It has been reported, for example, that retinal cells exposed to the hallucinogen LSD exhibit random and erratic behavior, in contrast to the systematic distortions produced by other drugs, such as nicotine (Ames, 1969). We have, therefore, attempted to test for such effects using a well known subjective color phenomenon as a measure of the changes that might be taking place.

When the eye is exposed to illumination, the resulting effects do not end as soon as the stimulation ends. Certain effects persist for some time. These are called "after-images." Among the most entertaining of these phenomena is the so-called "flight of colors." When the eye is exposed to a bright white light, one continues to see an image of the light after the illumination is turned off or greatly reduced. At first the color of this image is similar to that of the original, but it soon changes and begins a series of color transformations. The series may be predictable under strictly controlled conditions, but as Brown (1965) has noted, there is disagreement as to the colors reported and their order, because different investigators have used different conditions.

Little work has been done on the effects of drugs on chromatic after-images. Kaplan (1960) has reported effects of sympathomimetic and parasympathomimetic drugs on after-images, and Carr (1954) has reported a case of hallucination of color with the use of a methedrine inhaler. Malitz and Kanzler (1970) state that Dexedrine has no effect on after-image sensitivity.

This study sought to determine if the flight of colors is changed after the administration of the drugs.

Method

The subject was seated 1 m from a General Electric 150 W Photo-enlarger lamp, No. 212. This lamp has a white, frosted bulb which gives it an evenly illuminated surface. The lamp subtended roughly a circle 3.5 degrees visual angle (dva) in diameter and was seen through a 7 x 11 dva aperture in a dark gray cardboard .5 m wide and .75 m high. At an angle 30° to the right of the line of sight to the lamp was an adjacent sheet of light gray cardboard .75 m high and 1 m wide, illuminated to .002 ft-lamberts.

The procedure was as follows: The subject was first instructed in the nature of after-images and then told about the procedure. First he looked at the stimulus-light which was illuminated for 5 sec by a Hunter timer. As soon

as the light went off, he turned his gaze to the screen to the right of the light. He was instructed to report the color of the after-image immediately when signalled. He was signalled to respond at these times after the light went off: 5", 10", 20", 30", 40", 50", 60" and in quarter-minute intervals after that. The session was continued until he reported no after-image for three consecutive response-intervals. The experimenter made notes of the subject's responses, which were also recorded on tape. There were two sessions separated by about 15 minutes under both the drug and placebo conditions.

Results

The first question which can be asked is whether the drugs affect the duration of the train of after-images. Table IX gives the time in seconds at which the last report of any after-image - including black - was made. The final report was made at a later time for every subject under Valium. The mean increase of 30 seconds is significant ($t = 2.64$, $df = 11$, $p < .03$). The difference in mean duration between the two conditions was not significant for any other drug, although it is interesting that in every case, except that of Benadryl, the mean time was longer for the drug. It will be noted that the mean duration of the flight of colors was longer for the Valium-placebo group than for any other group to begin with, but these differences are not significant ($F = .60$, $df = 5/30$).

The next question concerns the description of the flight of colors. Let us first examine the after-images produced when the subjects were not under the influence of the drugs. All the responses were accumulated into the categories of purple, blue, green, yellow, orange, red and neutral (black, white, or gray). The frequency of each color-name was tabulated at each response-interval. Figure 4 shows the distribution of the color-responses in terms of the percentage of the total responses during that response-interval. The various colors clearly peak at different times after the stimulus-light is turned off, and different colors are most prominently reported at different times. During the first response-interval at a latency of five seconds, yellow was the most frequently reported color. But the frequency with which it was reported declined rapidly during the first minute, had a low frequency of report for the next minute and a half, and after that was never reported.

Red was reported much less frequently than yellow during the first response-interval, but its frequency of report rapidly increased for the first 40 seconds and then steadily declined.

Table IX. Mean time (sec) at which final report of an after-image was made

	Drug	Placebo
Aralen	146	133
Benadryl	130	136
Dexedrine	150	141
Digoxin	154	144
Valium*	195	165

* $p < .05$

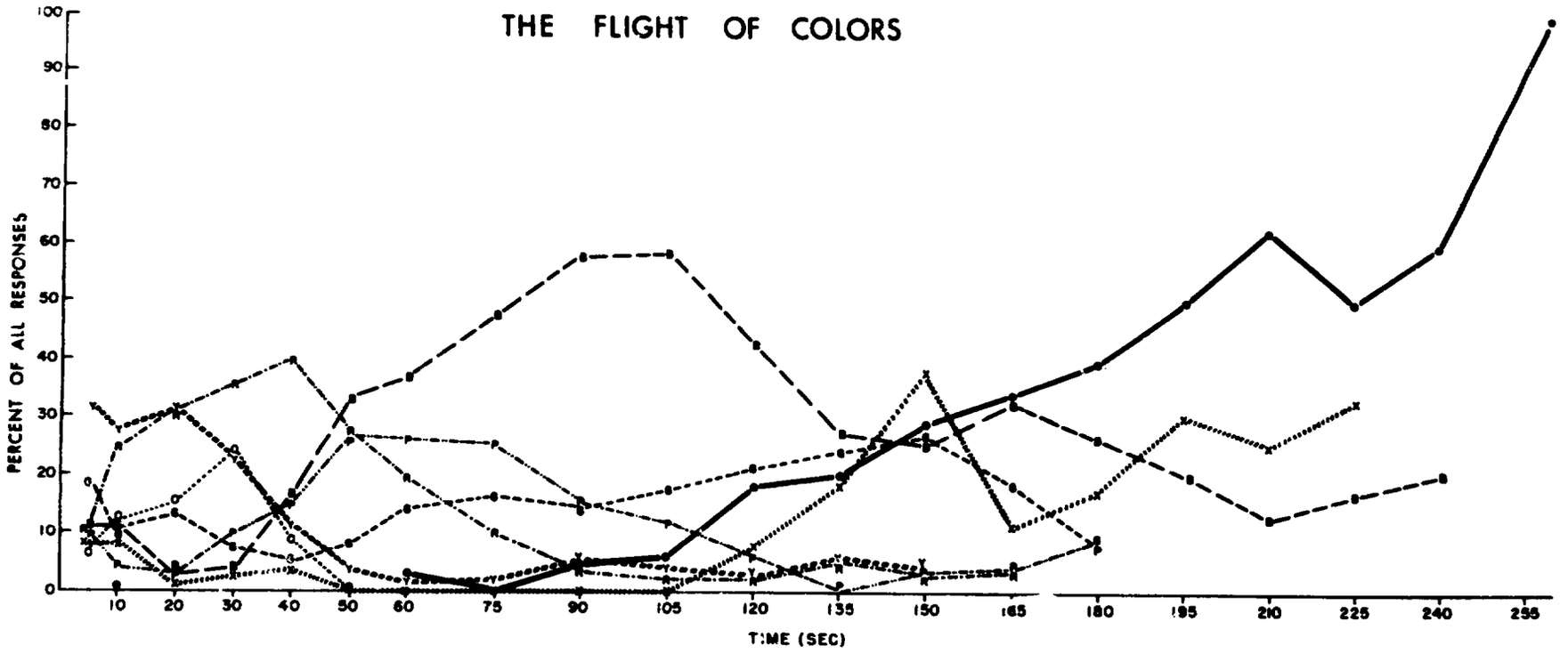

Fig. 4. The flight of colors. Each color frequency is the percentage of all responses at that response-interval. (P, blue; G, green; P, purple; R, red; Y, yellow; X, white; ●, black)

Blue did not reach a peak until 105 seconds. Black was reported very infrequently until nearly two minutes had elapsed, after which its frequency of report steadily increased until after four minutes it was the only color reported.

Table X gives the latency of peaking for the various colors, computed in two ways, (1) the percentage of reports for a given color in terms of the total reports for all colors in that response period, and (2) as the percentage of reports of that color during the entire session. The two sets of results are quite similar. Only the position of white is not consistent, due to the fact that there was a very small total number of white responses but they appeared throughout the session. The first color, yellow, is apparently the positive after-image of the stimulus-light. Next is orange - the yellow mixed with red. Next comes red, followed by purple, which is red mixed with the increasing amounts of blue.

Table X. Latency (sec) at which the various colors were reported with maximum frequency. Computed in two ways (see text)

	(1)	(2)
Yellow	5	5
Orange	30	30
Red	40	40
Purple	50	60
Blue	105	90
Green	150	75-105*
White	150	10-135*
Black	255	120

*Bimodal

Green and black are the last colors to peak.

Figure 5 shows the change in relative percentage of total reports for each color under the drug condition compared to its placebo condition. In the top half of the figure, the colors are organized for each drug. There were greater changes for Aralen, Benadryl, and Valium than for Dexedrine or Digoxin. The largest change for the latter was a mere 3.2% drop in the reports of green. Benadryl, on the other hand, produced an increase of more than 8% in the reports of blue.

In the bottom half of the figures, the same data are replotted with the changes organized by color for every drug. It can now easily be seen that every drug resulted in a decrease in the relative percentage of reports of "yellow" and every drug except Valium produced a decrease in green and an increase in red.

These mean values must be subjected to a temporal analysis, since it is possible that they conceal certain effects. It is possible, for example, that a mean change of zero actually masks an increase in the frequency of a given color during part of the session and a decrease at another part, the one cancelling out the other. Or, a mean change of zero may mask the fact that the entire frequency distribution of color-responses has shifted in time.

The set of reports of a given color can be analyzed in two ways, as noted above in connection with Table X. We can calculate the reports of a given color as a proportion of all the reports

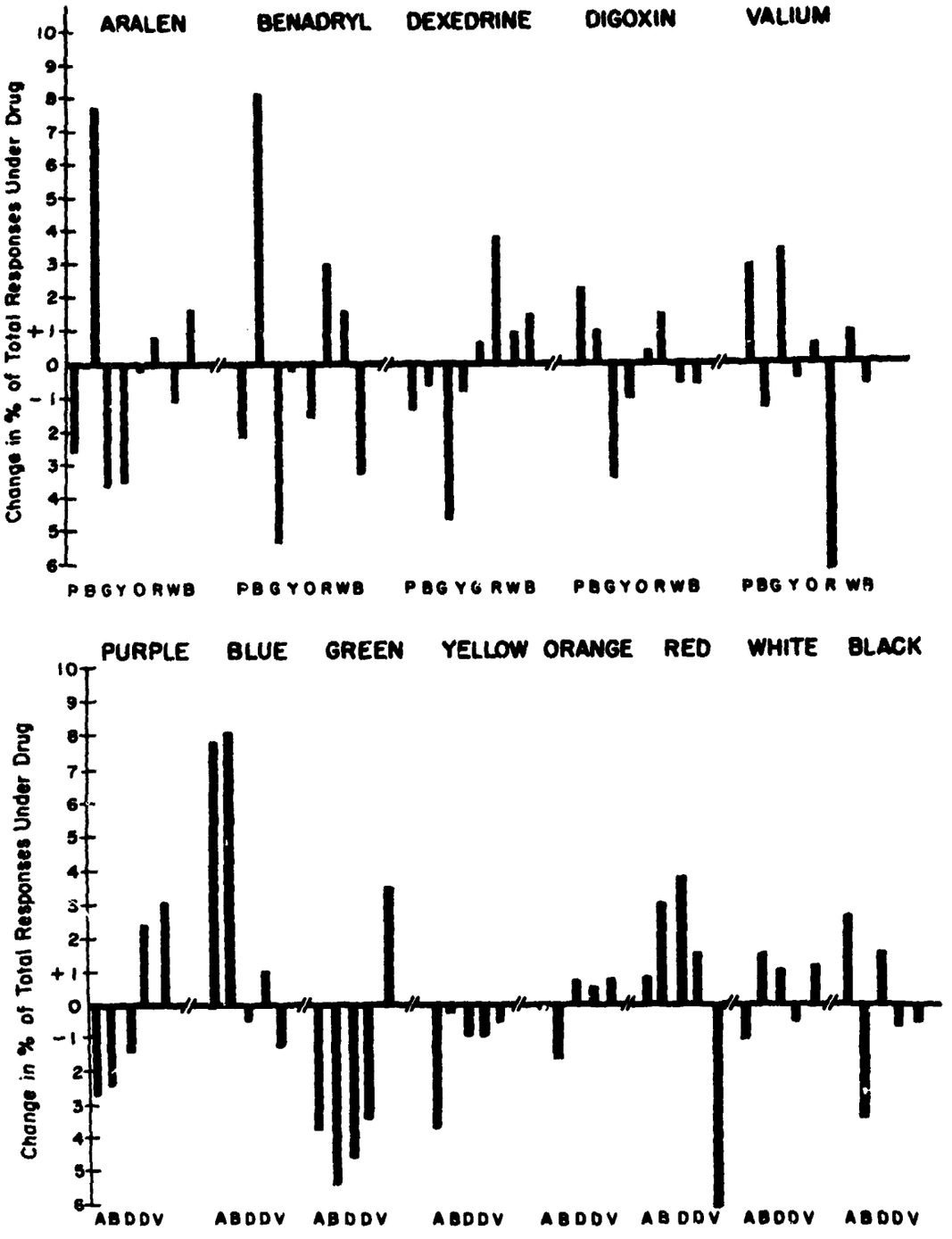

Fig. 5. Change in relative percentage of reports for each color under the drug compared to the placebo condition. The data are grouped by drug at the top and by color at the bottom.

for all the colors during a given response-interval. This tells how the proportions of the colors vary from one response-interval to another. It may show that at a certain time the highest proportion of reports were "red", but it does not tell us when the distribution of reports for a given color reached a peak. That is determined by taking the responses for a given color during a given interval as a proportion of all the responses for that color during the session. Thus we see how the responses of a given color are distributed throughout the session.

Both analyses were carried out. Again, the two sets of curves were quite similar. Only for the reports of "black" and "white", for both of which there were very few responses, were there substantial differences. The degree of similarity can be gauged from Table X, which gives the peaks for each color from the two sets of analyses; except for "white", the colors maintain not only their order but to a considerable extent their actual values as well. The presentation of the results will therefore be confined to only one of the analyses, the proportions of the total responses.

The proportion of the total reports represented by each color has been calculated at each response interval for each drug and its placebo group. The differences between these two sets of curves have been obtained for each color under each drug and plotted in Fig. 6 for every color except black and white.

Figure 5 has already shown that after the administration of Aralen there were no mean changes for orange and red, but the reports of purple were reduced by about 2.5%, green and yellow by 3.5% and blue increased by over 7%. Figure 6 shows, for example, that the decrease in reports for purple occurred only after the first 30 seconds; during the first half minute there was, on the contrary, a sharp increase in reports of purple. Similarly, the increase in total blue reports also reflects the results of the later segments of the flight of colors; for the first 20 or 30 seconds, there was a drop in the number of blue reports under the drug.

The curve for green appears to show only random fluctuations. That for yellow shows a decline in the yellow reports at a latency of 20-30 seconds.

Figure 5 shows virtually no mean change for orange; the temporal analysis shows, however, a marked decrease during the first two intervals followed by a marked increase immediately afterwards. Where there is an increase in orange, there was a decrease in red reports.

Similar analyses are easily made for the other drugs. It should be noted that these changes are not artifacts resulting from markedly different number of responses under the drug and placebo conditions. Although there was an increase in the number of responses with every drug, it amounted to an increase of only 1% for Benadryl, 2.6% for Digoxin, and 2.8% for Aralen. The increase was appreciable only for Valium (15.5%) and Dexedrine (12%) (Table XI). As noted above, the increase for Valium apparently resulted essentially from the increase in the duration of the after-images.

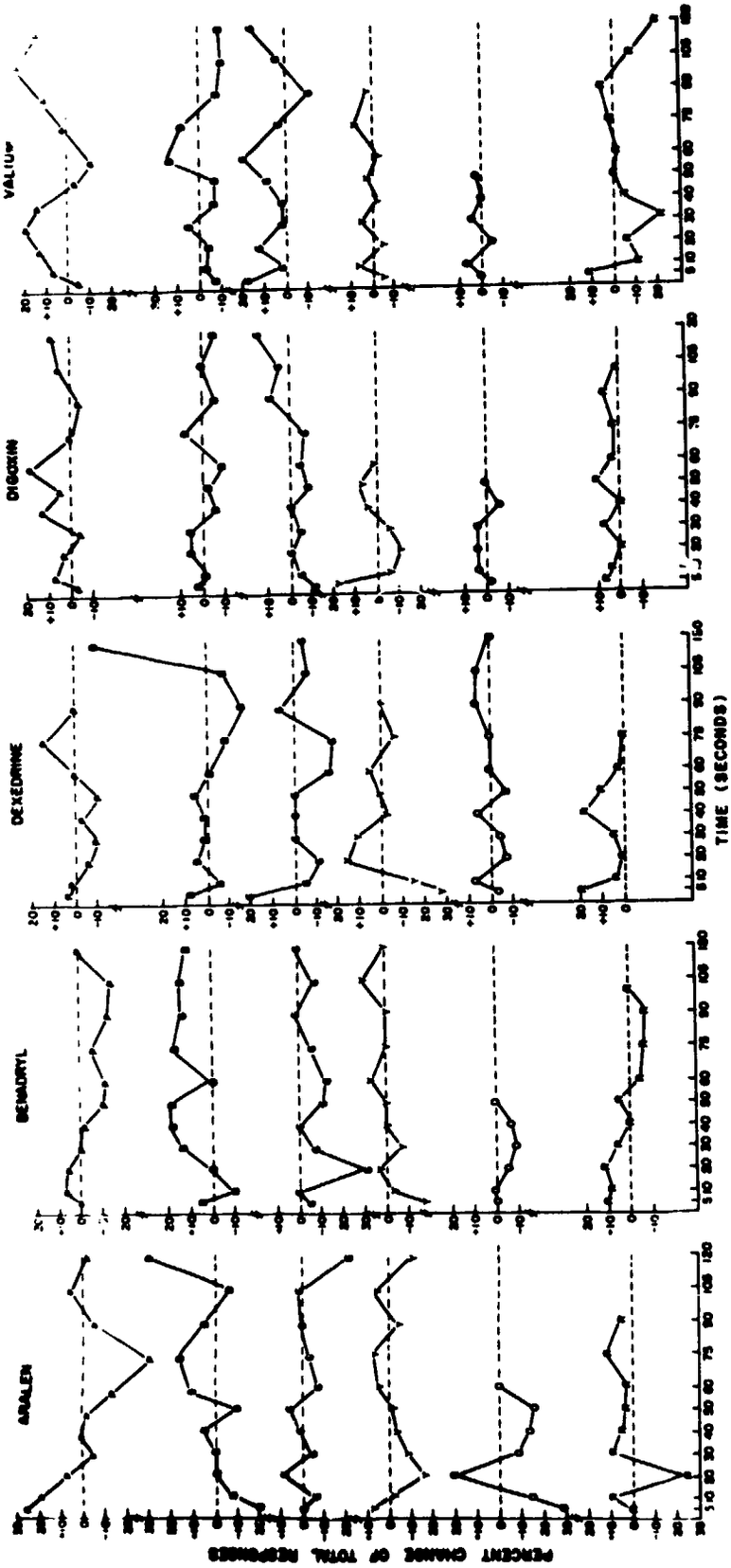

Fig. 6. Change in the frequency of report of each color, as a percentage of the total responses, at each response-interval for the drug condition compared to its placebo condition.

Table XI. Total number of reports of each color for each group under drug and placebo conditions

	Purple	Blue	Green	Yellow	Orange	Red	White	Black	Total
Aralen	23	56	34	27	7	43	11	17	218
Placebo	28	38	41	34	7	40	13	11	212
Benadryl	18	60	8	27	3	44	10	19	189
Placebo	22	44	18	27	6	38	7	25	187
Dexedrine	22	75	8	21	21	39	19	15	220
Placebo	22	67	16	20	17	27	15	10	194
Digoxin *	80	138	60	43	23	75	6	10	435
Placebo	69	132	74	46	21	67	8	12	429
Valium	23	71	23	28	13	39	6	27	230
Placebo	14	64	13	25	10	46	3	24	199

*two groups

Discussion

The essential aspects of the flight of colors in these results conform to previous findings. In her study of the flight of colors, Shuey (1924) reported that after strong stimulation the order of colors was yellow, red, blue, and green. This is also the order in which the primary colors appeared to our subjects. Our results also conform to Berry's (1927) finding that the initial color most frequently reported was yellow, and the next most frequently reported initial color was green. It has also been reported that color defectives do not report certain colors. Weve (1925) for example, stated that deuteranopes never report red or green. One of our subjects was deuteranomalous, one was protanomalous, and one was a protanope. The protanope never reported red.

There are differences between the present results and previous ones, but they are rather minor and can probably be ascribed to different procedure details. Berry reported the third most frequently reported color was orange; we found it to be red or blue, but the third color, whatever it is, is reported only about 10% of the time.

Also, Shuey reported that a 20-second exposure was too short to give reliable data; she used a 40-second exposure at various intensities. We, however, found a 5-second exposure of a 100-watt bulb to be quite adequate to produce the flight of colors. Shuey reported a mean duration of 3.5 minutes after exposure to a 100-watt bulb for 40 seconds; we obtained a mean duration of 2.5 minutes after 5 seconds exposure to a 100-watt bulb.

Our only statistically significant result was the increase in the duration of the flight of colors under Valium. As a result of this increased time, there was an increase in the number of reports made by the subjects. It is interesting to compare this result with that from Dexedrine, which produced an increased number of reports without reliably increasing the duration. Valium is, of course, a CNS depressant and would seem to have slowed down the nervous system processes, thus prolonging the flight of colors. Dexedrine, on the other hand, is a CNS stimulant and appears to have produced an increased rate of responding, without increasing the duration of the after-images just as in color discrimination. Dexedrine increased speed but not accuracy. These two results thus appear to be consistent, but it must be noted that Benadryl is also a CNS depressant, yet it did not prolong the after-images as did Valium.

There do not seem to be any clear-cut effects of the drugs on the more detailed aspects of the flight of colors. We have already noted that Valium was the only drug which produced a sizeable increase in red reports and an increase in green reports, but the reason is not clear. There are, however, a number of instances of decreases in red accompanied by increases in green and vice versa in Fig. 5, as well as examples of similar blue-yellow changes. Such results suggest a shift in the neutral point of an opponent colors system (Jameson and Hurvich, 1955) and it is interesting to speculate that one effect of drugs

might be to change the balance between the components in an opponent system.

BENHAM'S TOP

Among the most fascinating of the visual illusions are the perceptions of color that result from trains of brief stimuli that are only black and white. The best known device for producing such patterned stimulation is the disk, shown in Fig. 7, that is known as Benham's top. When this black and white disk is rotated between 5 and 10 rps so that it stimulates the eye with a series of different light-levels in rapid succession, most observers report seeing rings of different colors. The particular colors perceived depend on the direction and speed of rotation.

No definite explanation of this phenomenon has yet been accepted. Jameson (1972) has summarized five types of explanation and remarks that there is probably some validity to all of them. Most, of course, relate to the workings of the nervous system. They postulate for example, that the colors result from lateral interactions of nervous impulses, or that the pattern of nerve impulses is the physiological code for hue. Since several of these drugs either stimulate or depress the nervous system, and since color-effects are widely reported to be a symptom of the drugs, we have measured the subjective colors aroused by the Benham's disk.

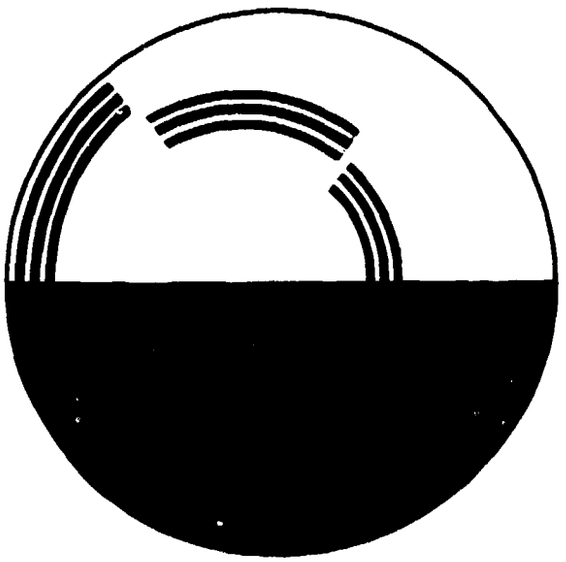

Fig. 7. Benham's Top

Method

The disk used in this study was 30.4 cm (1 ft) in diameter and each line was 2 mm thick. At the viewing distance of 1.5 m, the disk subtended a visual angle of 11.5°. It was positioned in a large compartment and was viewed through a square aperture, 1 m from the subject, which subtended about 12° visual angle. The disk was mounted before a white background illuminated to 100 ft-L by four tungsten lamps, one behind each corner of the viewing window. Judgments of the colors were made at two clockwise speeds of rotation, presented in random order of 6 and 10 rps, as calibrated by a General Radio Strobotac, Type No. 631-B. The speed of rotation was controlled by a General Radio Variac, Type No. 1701-AK.

To report his subjective colors, the subject matched them to a sample "chip" in the Munsell Book of Color (Munsell, 1929). At each speed of rotation, he selected three Munsell chips, corresponding to the color seen in each of the three sets of rings on the disk. The Munsell Book was placed on a desk immediately in front of him and

illuminated to 4 ft-L by a Macbeth Daylight lamp.

Results

The effectiveness of the disk in producing perceptions of color in the placebo conditions is indicated in Fig. 8. This gives the frequency with which the six color-names (including gray or neutral) used in the Munsell Book of Color were chosen by the 36 subjects to match the colors they perceived. The results are given for each of the three sets of rings on the disk at the two speeds of rotation. The most prominent color seen in the outer rings at both speeds was yellow, with some green and red. Yellow was also the most prominent color in the middle rings, but it is clear that the hues are shifting toward the shorter wavelengths. The frequency of the green reports increased and there were an appreciable number of blue reports as well. In the inner rings, on the other hand, green and yellow have virtually disappeared; purple-blue is the predominant color, with some red reports.*

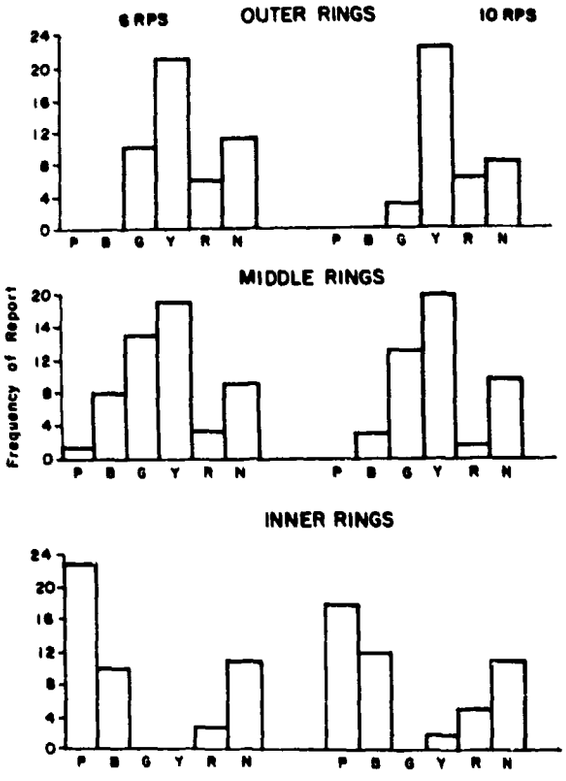

Fig. 8. Frequency with which various colors were reported seen in the three sets of rings on Benham's top (P, purple, B, blue; G, green; Y, yellow; R, red; N, neutral).

The selected Munsell chips were specified as C.I.E. tristimulus coordinates (Kelly et al, 1943; Granville et al, 1943; Nickerson et al, 1953) and the mean coordinates of the sets of rings at both speeds are plotted on the C.I.E. diagram in Fig. 9. On the average, the colors reported were rather desaturated.

Figure 10 shows the mean tristimulus coordinates for each group of subjects under the drug and placebo conditions at both speeds. Consider the results for the outer rings at 10 rps. The five filled circles, the results of the placebo conditions, clearly fall in a straight line which intersects the spectral locus at about 575 nm, a slightly greenish-yellow. The fact that these points fall along a straight line indicates that the five groups of subjects are, on the average, varying only in their mean judgments of saturation, not in the hue

*If plotted as a color circle, of course, the red would be adjacent to the purple.

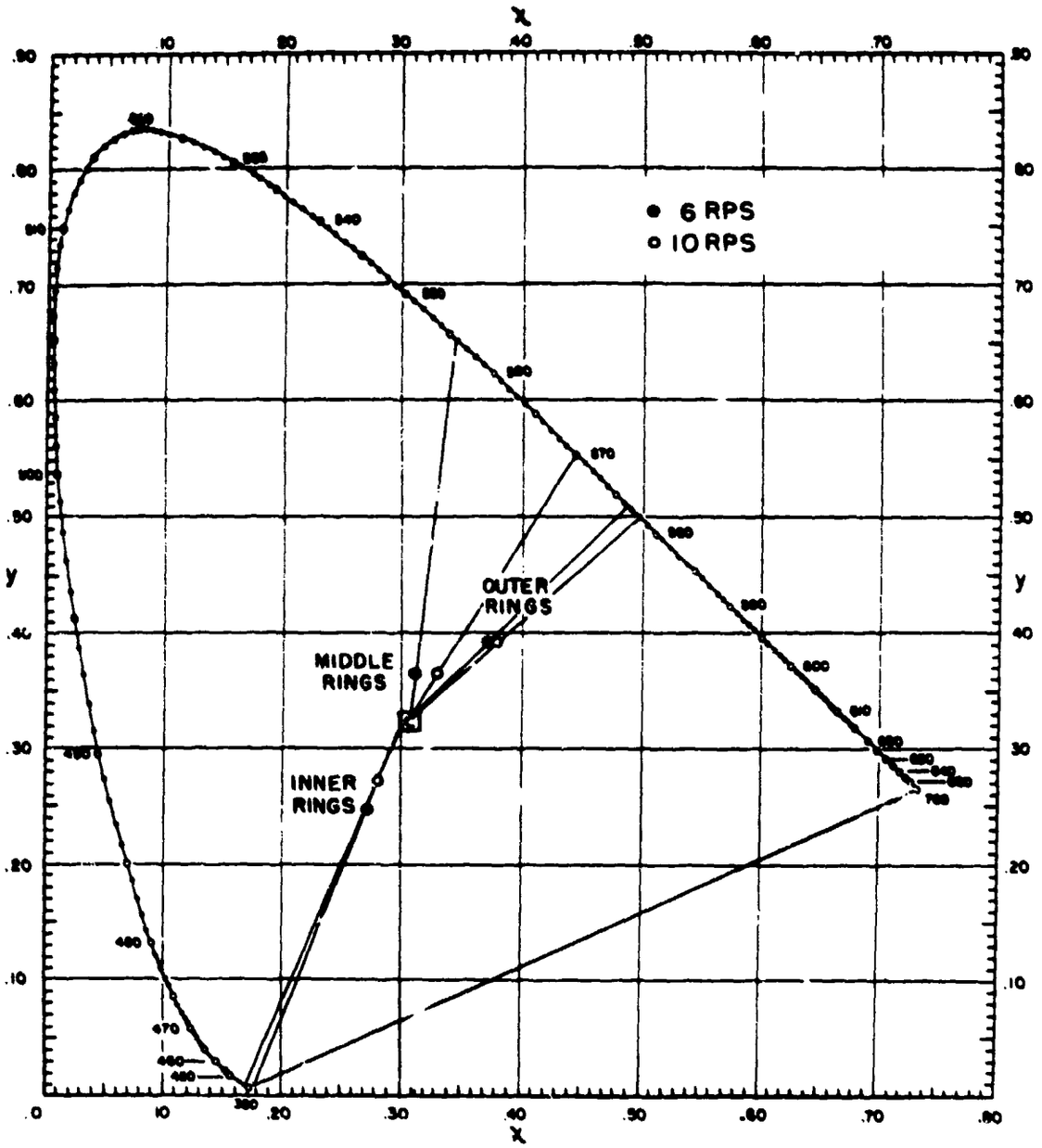

Fig. 9. Mean C.I.E. coordinates of the Munsell color samples chosen as a match to the colors seen in the three sets of rings on Benham's top by the subjects in the placebo condition.

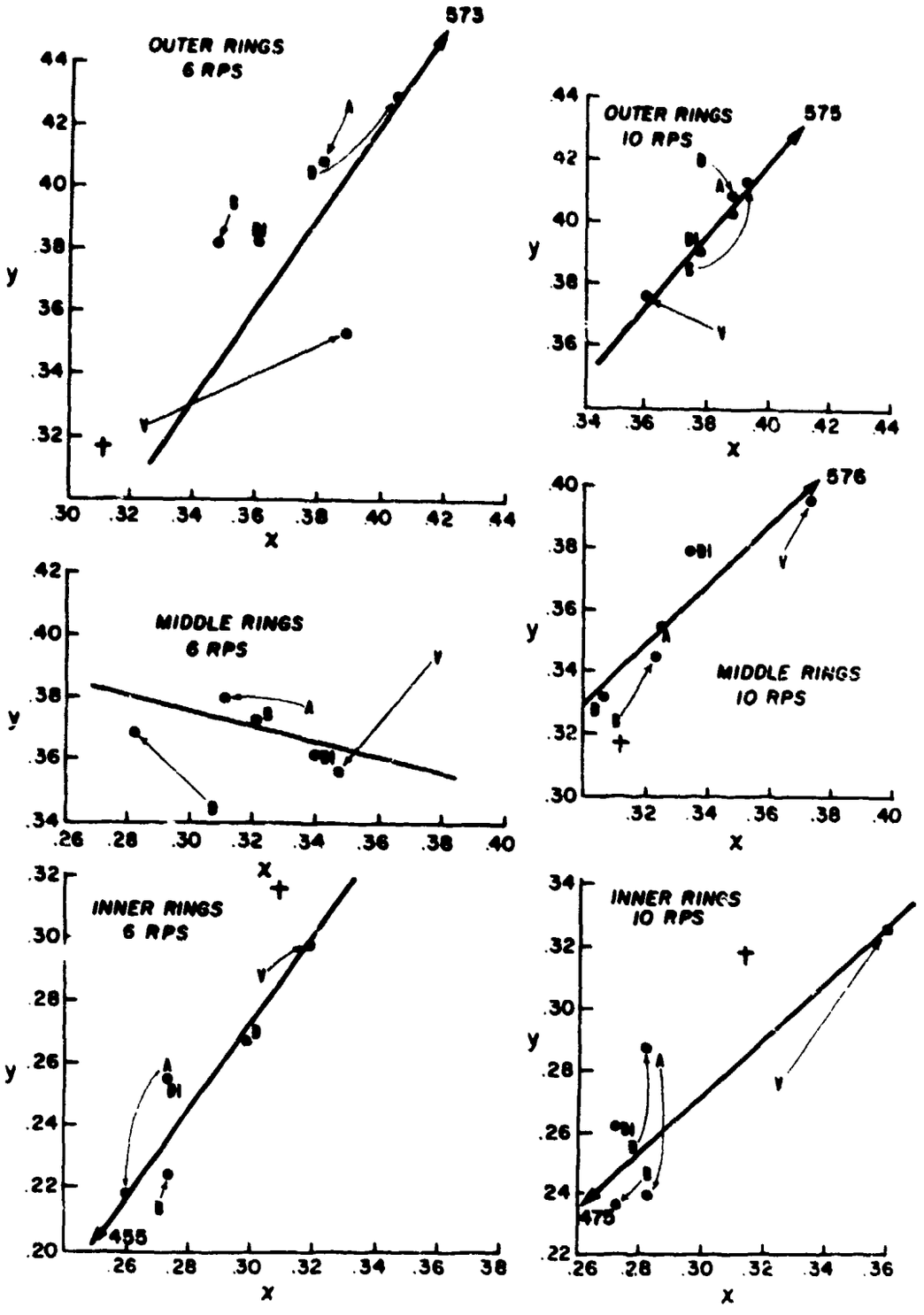

Fig. 10. Mean C.I.E. coordinates of the Munsell color samples chosen to match the colors seen in the three sets of rings on Benham's top under both speeds of rotation by each group of subjects under both drug (letter) and placebo (filled circle) conditions. (A, Aralen; B, Benadryl; D, Dexedrine; DI, Digoxin; V, Valium)

which they are perceiving. Similarly, the sets of placebo points in the other panels of the graph also appear to describe straight lines which, except for the results for the middle rings at 6 rps, intersect the spectral locus approximately where expected on the basis of the frequency distribution in Fig. 8. The mean coordinates for the drug groups (letters) are generally displaced only slightly from the placebo regression lines.

The shifts, however, are not systematic. When each mean drug value is compared with its placebo point, two of the points for Aralen, Benadryl and Dexedrine change in the direction of more saturation, and four become less saturated. For Valium, three changes are toward more saturation. When a similar comparison is made by subject (Table XII), the shifts are also completely random.

In addition to analyzing changes in saturation, we have tabulated the change in dominant wavelength after administration of the drugs. The changes after each drug are accumulated for both speeds and for the three sets of rings in Table XIII. Typically, there were relatively few hue changes. For Aralen and Benadryl, there were roughly equal shifts toward longer and shorter wavelengths. For the other three drugs, there were roughly twice as many shifts toward the longer as toward the shorter wavelengths. However, an analysis by individual subjects for each condition shows that in no case did as many as four subjects show the same effect under any given speed and set of rings.

Discussion

Benham's top clearly produces the perception of specific hues in each series of rings. There is no evidence, however, that any of the drugs produces such changes as increased saturation of chromatic perceptions, or shifts in the

Table XII. Changes in saturation of subjective colors under each drug in the various sets of rings under both speeds

Drug	More saturated	Less saturated	Same
Aralen	15	13	8
Benadryl	12	15	9
Dexedrine	12	14	10
Digoxin	28	24	17
Valium	13	13	10
Totals	80	79	54

Table XIII. Hue shifts on Benham's Top under each drug accumulated for both speeds of rotation and three sets of rings

Drug	Towards longer wavelengths	Towards shorter wavelengths	No hue shift
Aralen	8	5	22
Benadryl	9	8	19
Dexedrine	10	5	21
Digoxin	25	13	34
Valium	13	5	18

dominant wavelength of the perceived hue, as has often been reported for other kinds of phenomena. The mean directions of the shifts for each drug, as well as the pattern of shifts for each subject with a given drug, did not approach statistical significance in any instance. The skew of the total distribution of hue shifts toward longer wavelengths under Dexedrine, Digoxin, and Valium is interesting, but the analysis of individual data did not approach statistical significance.

ELECTRICAL ACTIVITY OF THE BRAIN: EEG and VER

A great deal of effort is being made to determine the effects of drugs on visually evoked responses (VERs) and on the electroencephalogram (EEG). The immediate benefit is that these measures reflect the state of the central nervous system, and monitoring VERs and EEGs during the administration of a drug has been shown to be useful in studying adaptive mechanisms to drugs which affect the CNS (Khazan et al, 1967; Khazan and Colasanti, 1971).

A further goal is to be able eventually to analyze the functioning of the nervous system and monitor the effect of drugs at various neuroanatomical sites (Regan, 1972). Another goal is to help in the prescription of drugs to alleviate specific behavioral or neural disabilities. The achievement of these goals would be of great practical importance.

To give one example, it has been found in studies of divers that VER changes accompany nitrogen narcosis: Decrements in VERs have been found for divers breathing air at depth - which results in nitrogen narcosis - but not for divers at the same depth breathing a mixture of helium and oxygen - which does not result in nitrogen narcosis (Kinney et al, 1972a; 1974). When VERs are monitored at different locations in the brain, the decrease in amplitude is not of equal magnitude everywhere (Bartus, 1973). Such analyses may suggest the possible sites and mechanisms of nitrogen narcosis and eventually lead to a better understanding of how it may be prevented. Bergamasco (1967) has concluded that "the study of cortical reactivity is a new parameter for neuro-pharmacological investigation in man." And Shagass (1968) has summed it up by saying, "It seems indisputable that the evoked response method offers much promise as a contributor of valuable information in psychopharmacological investigations."

Although much of the interest about the various effects of drugs has centered on the psychoactive drugs, a number of studies have investigated the effects on VERs and EEG of four of the five drugs used in the present study. Many of the previous studies have dealt with Valium. Gibbs and Gibbs (1962), Towler (1962) and Kooi (1971), for example, note that it results in an increase in fast activity in the EEG, which replaces alpha. At the same time, visual evoked potentials are reduced in normal humans (Broughton et al, 1966; Bergamasco, 1967; Poire et al, 1967; Ebe et al, 1969)* leading Poire et al to

*Similar reductions have also been reported in cats (Requin et al, 1963; Sherwin, 1971) rabbits (Arrigo et al, 1965), and rats (Olds and Baldrighi, 1968). Heiss et al, (1966) reported increased latency in cats.

conclude that "Valium considerably diminishes physiological potentials evoked by light in man."

Benadryl has been reported to have "no effect on the EEGs of normal individuals, although it has a variety of effects on patients exhibiting various abnormalities in their EEGs (Diaz-Guerrero et al, 1956). Fink (1968; 1969), however, states that it increases slow frequencies in the EEG. Friedlander (1961) also notes that Benadryl induces sleep EEGs - not surprising since Benadryl is reported to be the most effective of the antihistamines in inducing drowsiness (Goodman and Gilman, 1960). Churchill and Gammon (1949) report a decrease in diffuse 3 cps waves in patients suffering from true petit mal epilepsy. Frank and Jhamandas (1970) report that Benadryl depresses surface negativity in cats.

Dexedrine has been reported to increase the frequency of the EEG and reduce slow activity (Mule and Brill, 1972). Shetty (1971) found that it decreased photic driving in hyperkinetic children. Marazzi and Hart (1953) and Domino and Corssen (1964) reported no effect on evoked responses. Tecce and Cole (1974) have found that Dexedrine lowers contingent negative variation in some individuals and raises it in others.

Torrey (1968) points out that "little work has been done on the effects of chloroquine on the EEG." Of the three cases which he reported on, only one was abnormal; he cites the work of Wada and Yoshida to the effect that when chloroquine was used with other drugs in the treatment of epilepsy, "there was a tendency toward normalization of EEG in 60 cases.." Kooi (1971) notes that Aralen, given in high dosage over a period of time, has been reported to result in an increased beta response in the EEG.

We have come across no studies dealing with the effects of the digitalis group on the electrical response of the brain.

Method

EEGs were recorded from bipolar electrodes located at O_Z, T_5, C_3 and F_7 with a ground electrode on the subject's ear; VERs were obtained between O_Z and C_3. O_Z lies over the primary visual projection area, and the other three electrodes were placed to monitor the frontal and temporal regions. The signals were amplified by a Grass P511 preamplifier, simultaneously recorded by a Hewlett-Packard FM Instrumentation Recorder, Model 3960, and analyzed on line for evoked responses by a Technical Measurement Corporation Computer of Average Transients (CAT 400C).

The EEGs were transferred from tape to a Beckman polygraph, spot checked for artifacts, and analyzed by a Federal Scientific Spectrum analyzer and averager; this equipment produces curves of the average amplitude at each frequency from 0 to 50 Hz in 1/4 Hz steps for one minute intervals of EEG.

To obtain an evoked response, 100 one-second intervals of cortical activity following the onset of a stimulus were summed by the CAT; these were automatically counted by a TMS pre-set sweep counter. Paper records of the

evoked responses were printed by a Bolt, Beranek and Newman Plotamatic X,Y Recorder; from these records, measures of amplitude and latency of all components were made. It is also possible to sum the responses to one stimulus and then subtract the responses to a second stimulus to obtain an immediate record of the difference between the two sets of responses. This was done for two of the targets, in order to obtain a pattern response (White, 1969).

Targets - Four square targets, 10° on a side at the viewing distance of 1 m, were used to evoke the cortical responses. Three were either solid red, green, or blue, the fourth was blue and purple checkerboard whose individual squares subtended 30 min. All targets were of equal reflectance. Table XIV gives the color-specifications.

Recordings - Evoked potentials were first obtained in response to the solid colors, red, green, and blue, at a flash rate of 1 per second. Next, the response to the patterned stimulus was measured by subtracting the response to the blue-purple checkerboard from the response to the blue target. Third, responses were obtained to the red target presented at the rapid rates of 12, 16, and 24 flashes per second (fps). These stimulus conditions were chosen because previous studies had shown them to be sensitive measures of both pattern and color response and of stress (Kinney et al, 1972b, 1973; Kinney and McKay, 1974).

Finally, EEG records were obtained with the subject's eyes open and closed.

Table XIV. C.I.E. chromaticity coordinates of the targets

Color	x	y	z
Red	.5404	.2972	.1624
Green	.2248	.3506	.4246
Blue	.1996	.2265	.5739
Purple	.2760	.1979	.5261

Results

EEG

The EEG responses from the four electrode locations, using the ear as a reference, as well as bipolar responses from the frontal-temporal and temporal-occipital pairs of electrodes, were analyzed for amplitude of alpha waves with the subjects' eyes closed. The mean amplitudes under both drug and placebo conditions are given in Table XV. Several of the drugs reduced the amplitude of alpha in most electrode locations. All of the mean amplitudes were smaller with Benadryl; a paired t-test for the six pairs of values shows the differences to be significant ($t = 2.69$, $p < .05$). In addition, an analysis of variance shows that differences at the O_Z and T_5-O_Z locations are significant. For Digoxin, also, an analysis of variance showed that the alpha amplitude decreased significantly in three of the electrode placements: the paired t-test was also significant ($t = 2.98$, $p. < .05$).

Evoked Responses

1. Color - both the amplitudes and latencies of the first major component of

Table XV. Mean alpha amplitude with eyes closed (μv)

Electrode Placements	Aralen N=6		Benadryl N=6		Dexedrine N=6		Digoxin N=10		Valium N=4	
	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug
F_7	3.48	3.48	4.13	3.95	3.72	3.28	3.39	3.39	2.74	2.40
C_3	5.00	5.00	5.84	4.96	5.68	4.80	5.10	4.78	2.72	2.69
T_5	8.92	7.88	5.96	5.74	6.32	4.44	6.36	4.78*	4.05	2.30
O_z	9.92	8.92	8.13	4.40*	8.20	7.20	7.22	6.06*	4.18	3.72
F_7-T_5	9.88	8.32	8.06	6.18	7.32	6.72	8.23	6.00**	4.26	3.51
T_5-O_z	4.40	7.68	5.70	3.55*	5.68	5.08	4.81	4.07	3.87	3.55

* $p < .05$

** $p < .01$

the visual evoked responses to the three colors were compared in the drug and placebo conditions. There were no discernible trends in the amplitude changes under any of the drugs, and no trends in the latency changes for any drug except Dexedrine. The latency of the major component was 5 msec shorter under Dexedrine for all six subjects in response to the red target. The difference was statistically significant according to a paired t-test ($t = 3.80$, $df = 5$, $p < .02$).

2. Pattern - When the evoked response to the blue-purple checkerboard pattern is subtracted from that of the blue target, a difference-curve with two major components is obtained: there is a peak at around 165 msec and a dip at around 225 msec (Fig. 11). Both the amplitude and latency changes under the various drugs were compared with the placebo results. Again, the only changes which were statistically significant occurred with Dexedrine; the latency of both sets of components was

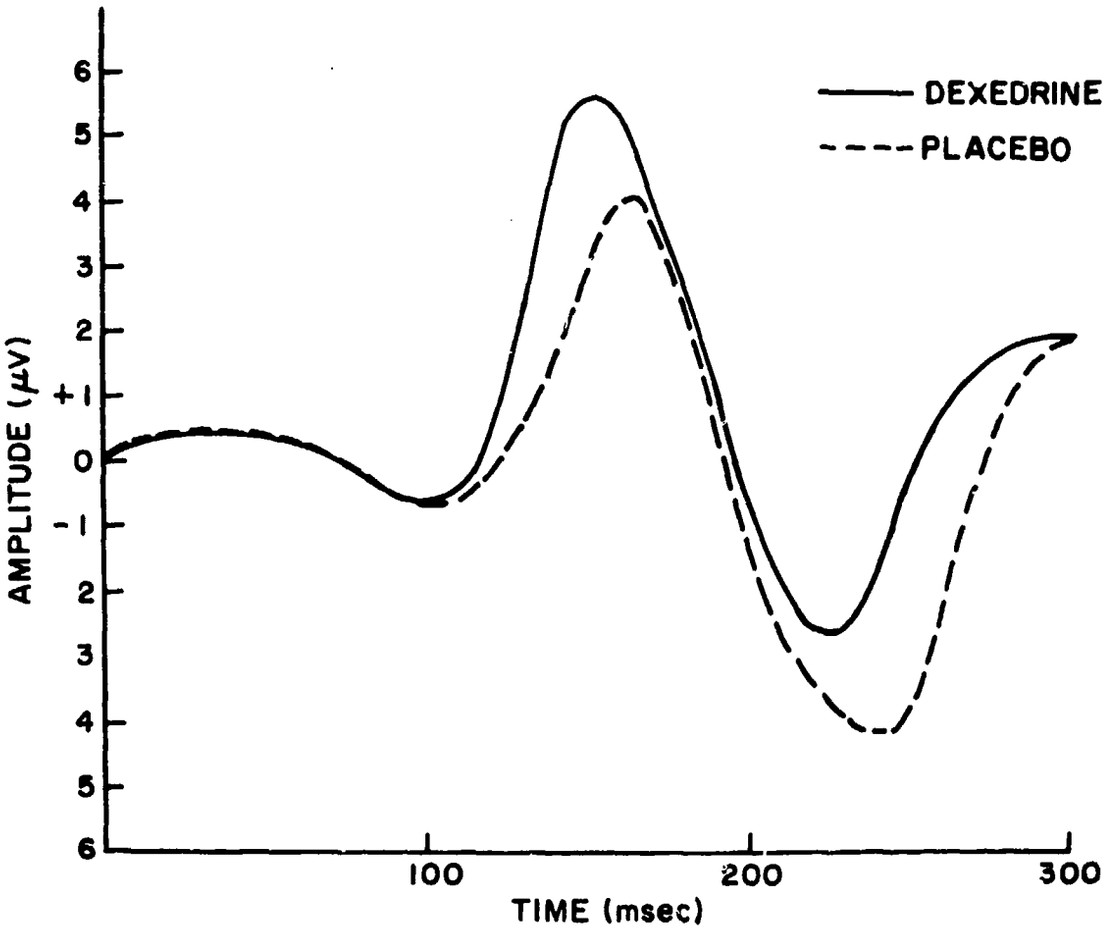

Fig. 11. Visual evoked responses to a blue-purple checkerboard pattern subtracted from the visual evoked responses to a blank blue stimulus under Dexedrine and its placebo condition

shorter under the drug, 10 msec on the average for the first component and 14 msec for the second component ($F = 152.6$, $df = 1,5$, $p < .01$). In only one of the 12 pairs was the latency longer in the placebo condition (paired $t = 4.35$, $df = 11$, $p < .01$). No other results were statistically significant, but the amplitudes of the components were smaller for five of the six subjects under Aralen.

3. Rapid Flash Rates - The responses to rapid flash rates were analyzed for mean amplitudes of responses ($\bar{X}$), standard deviation of the amplitudes (σ), and for the regularity or consistency of the amplitude through the train of responses ($\bar{X}/\sigma$). For example, Figure 12 shows examples of a more and less regular train of responses to the flashing light. No changes in regularity were statistically significant.

There were two instances of statistically significant amplitude changes resulting from the drugs. The amplitude of the 12 fps response decreased under Aralen (paired $t = 3.22$, $df = 5$, $p < .05$), and the response to the 16 fps increased under Dexedrine ($t = 2.61$, $df = 5$, $p < .05$). In addition, of the five subjects for whom there was complete data for Benadryl, all had bigger amplitudes to the 24 fps. Similarly, under Dexedrine, five of the six subjects had increased amplitude to 12 fps. Table XVI gives a summary of the evoked response results.

Discussion

The main effect on the EEGs was the reduction in the amplitude of the alpha waves under both Benadryl and Digoxin. The statistically significant decrease in the amplitude of the alpha waves in response to Benadryl is not surprising. As noted above, Benadryl is said to be the most effective antihistamine in producing drowsiness and Friedlander (1961) has reported that it induces "sleep EEGs."

Table XVI. Summary of evoked response results

Drug	Color	Pattern		Rapid Flash rates
		1st component	2nd component	amplitude
Aralen	-	5/6 smaller	5/6 smaller	smaller to 12 fps*
Benadryl	-	-	-	5/5 larger to 16 & 24 fps.#
Dexedrine	latency to red shorter	latency shorter**	-	larger to 16 fps* 5/6 larger to 12 fps.
Digoxin	-	-	-	-
Valium	-	-	-	-

** p <.01
* p <.05
# p <.10

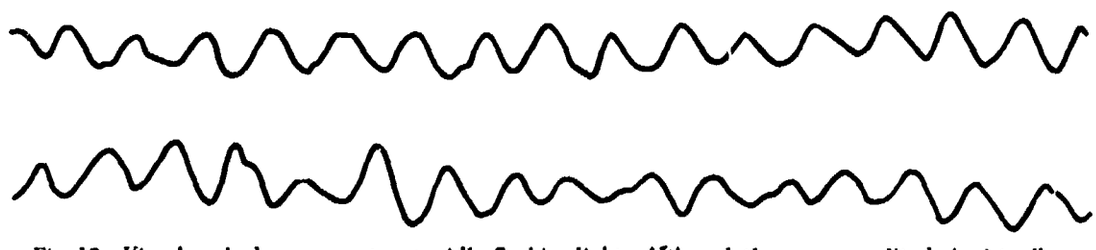

Fig. 12. Visual evoked responses to a rapidly flashing light. Although the mean amplitude is virtually identical, the upper curve shows a more regular train of responses (Z=4.80) and the lower curve a less regular train (Z=2.75). Both curves are from the same subject under Aralen (top) and the placebo.

We found no effects of Valium on EEGs in this study. Towler's (1962) results provide one reason. He found that the administration of Valium in doses of from 5 mg twice a day to 10 mg four times a day did not produce EEG changes until five days had elapsed. Further, Gibbs and Gibbs (1962), who reported that Valium had an effect, administered 30 mg/day. Both the dosages of Towler and Gibbs and Gibbs, of course, far exceeded our single dose of 5 mg.

The main effect on the VERs was the reduction of latency produced to both colored and patterned stimulation, and the increase in amplitude to fast stimulation produced by Dexedrine. This is also not surprising, since Dexedrine is a CNS stimulant. The only other significant result was the reduction in amplitude produced by Aralen. There was a tendency for Benadryl to increase the amplitude of the VER response to rapid flash rates. There have been no previous reports of such effects to our knowledge, although Rickards et al (1973) reported that other muscle relaxants did not reduce the amplitude of auditory evoked responses.

Finally, there was no indication of the reduced amplitude of VERs widely reported to be produced by Valium. However, in every investigation which found such reductions, Valium was injected intravenously and the dosage (when specified) was 10 mg, twice our present dosage.

EYE-MOVEMENTS

There have been very few studies of the effects of drugs on eye-movements. Most of the studies have been concerned with the effects of barbituates on tracking or accommodation-convergence. Norris (1968) lists the references to that date.

Yet it would seem that eye-movements would serve as an indicator of low levels of toxicity and give a very sensitive measure of psychomotor performance. Indeed, eye-movements have apparently long been studied in relation to schizophrenia (Holtzman et al, 1973: Stevens, 1974).

We are aware of only two studies carried out using any of the drugs in the present study. Westheimer (1963) tested the effects of amphetamine. He found that it enhanced the ratio of accommodative convergence to accommodation but did not change the absolute amplitude of accommodation. Gentles and Llewellyn Thomas (1971) found that Valium decreased the velocity of saccades.

In this study, two sets of eye-movements were recorded and analyzed. The first set was obtained with the subject simply maintaining fixation on a moving dot. In the second procedure, eye-movements were recorded as the subject scanned a panel of dials in search of a target-dial. The first set of data was obtained on all subjects. The second procedure was carried out only during the second half of the study. There are, therefore, data on only three of the drugs.

Method

The first procedure measured the subject's ability to maintain steady fix-

ation and to track a moving dot. A standard pattern of movement was prepared on movie film. The target on which the subject was instructed to maintain fixation was a dot .17° visual angle in diameter. The following sequence of movements was presented: First, the dot was presented for two seconds at the center of each edge of the screen. This pattern of fixations served to calibrate the subsequent printed record of the eye-movements. Next the dot was presented motionless in the center of the screen and the subject was instructed to keep his eyes as motionless as possible during that time. Then followed a series of saccades. The dot was presented at various locations for about three seconds at each position. The subject was instructed to follow the dot as quickly and accurately as possible. The movements of the dot entailed saccades ranging from 2 to 13°. Next the dot described four cycles of a sinusoidal wave moving from left to right; each of the cycles subtended 5° horizontally and 6.5° vertically. Finally, the calibration display at each of the four sides of the screen was shown again.

The subject viewed the movie with his head in a chin-rest, sitting at a distance of 170 cm from the screen.

During the second procedure, the subject sat behind a shutter with his head in a chin-rest 60 cm from a panel of 16 white dials (6.2° W x 5.7° H) arranged in a 4 x 4 rectangular array (60 x 34°). The vertical separation of the dials was 3.75° and the horizontal separation as 12°. Ambient illumination was provided by fluorescent ceiling lights.

The subject's task was to find as quickly as possible that dial whose reading was zero. To start a trial, the experimenter selected the pre-determined target-dial, opened the shutter, and pressed the "start" button. This turned on the timer, signalled the recorder and caused the pointer on every dial except the target-dial to move one-third of the full scale deflection. As soon as the subject found the dial which had not been activated, he pressed a button which returned every dial to zero, stopped the timer, and signalled the recorder that the trial was The experimenter closed the shutter and the subject reported the number of the target-dial to ensure that he had found the correct one. A session consisted of 16 such trials, with each dial in the array presented as the target in random order. A different random order was used on every occasion.

Eye-movements were measured with a Biometrics, Inc. Eye-Movement Monitor, Model SGHV-2 and recorded on magnetic tape by a Hewlett-Packard FM Instrumentation Recorder, Model 3960. Paper records were made with a Houston Instruments Omnigraphic Strip Chart recorder, Model 3000, and a Bolt, Beranek, and Newman Plotamatic X,Y Recorder. Search-times were timed with a Lafayette Instrument Co. Clock-counter, Model 54417.

Results

Table XVII presents the results of three analyses of the eye-movements made following the moving dot. It gives, first, a measure of the ability of the subjects to maintain steady fixation. The half-minute of steady fixation was

Table XVII Eye-movement measures

Drug	Fixation drift, deg)		Saccade error(deg)		Saccade Time (ms)	
	Drug	Placebo	Drug	Placebo	Drug	Placebo
Aralen	0.64	0.63	0.85	0.97	356	330
Benadryl	1.46	0.44*	1.37	0.83*	480	358*
Dexedrine	0.91	0.47	0.94	1.19	402	495
Digoxin	0.62	0.72	0.59	0.79	282	272
Valium	0.58	0.53	0.89	0.82	447	260**

* $p < .05$
** $p < .10$
+ 5/6

divided into 1.5 second segments, and the maximum range of subject's eye-movement during each segment was measured. The excursions in the final 10 segments in which no blink occurred were averaged to give the mean "fixation drift." There was an increase in the mean fixation-drift during the attempt to maintain steady fixation under Benadryl (Table XVII). Only one subject did not show an increase under Benadryl. Figure 13 shows typical 5 second segments of the eye-movement records from the subject with the highest and lowest magnitude of increase. (The large increase under Dexedrine was due to the data from only one subject and is not significant.)

The accuracy and speed of the saccades were also measured. When a saccade is made, the eye typically does not move directly to the desired end-point. There is usually some degree of under- or over-shoot, followed by corrective movements, until the eye is eventually more or less stablized on the new target. To calculate the saccade-error, the discrepancy between the first pause made during the saccade and the stabilized end-point was measured. Only Benadryl produced an appreciable change; every subject showed an increase in mean error under the drug.

Finally, Table XVII shows the mean time required to stabilize fixation on the new position. Once again, Benadryl

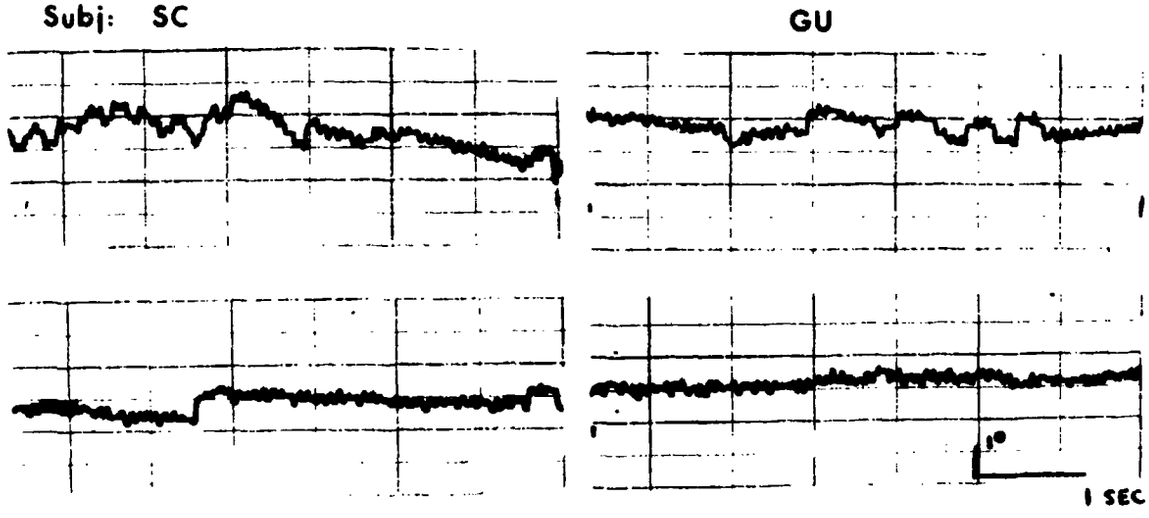

Fig. 13. Typical 5 second segments of recordings of eye-movements during attempted steady fixation under Benadryl (top pair) and placebo (bottom pair) for the subject with the largest (left) and smallest increase in magnitude of movement under the drug.

produced an increase in the mean value for 5/6 subjects. An increase under Valium, also occurred for every subject and was highly significant. Figure 14 gives an example of differences in saccade-error and time to stabilization.

No attempt was made to quantify the recording obtained as the subjects tracked the sinusoidal motions. However, our impression is that tracking under Aralen appeared to be somewhat degraded and improved under Dexedrine. Figure 15 shows four samples of these pairs of records for each drug.

Table XVIII gives the mean search-times in the monitoring study alongwith the mean duration of the fixations during the search for the target-dials in the second half of the study. Mean search-times decreased slightly under every

Table XVIII. Mean search-times (sec) and fixation-durations (sec) during search for target-dials.

Drug	Search-time		Fixation-duration	
	Drug	Placebo	Drug	Placebo
Aralen	3.69	4.05	.348	.343
Dexedrine	3.16	3.49	.306	.318
Digoxin	3.77	4.03	.334	.346

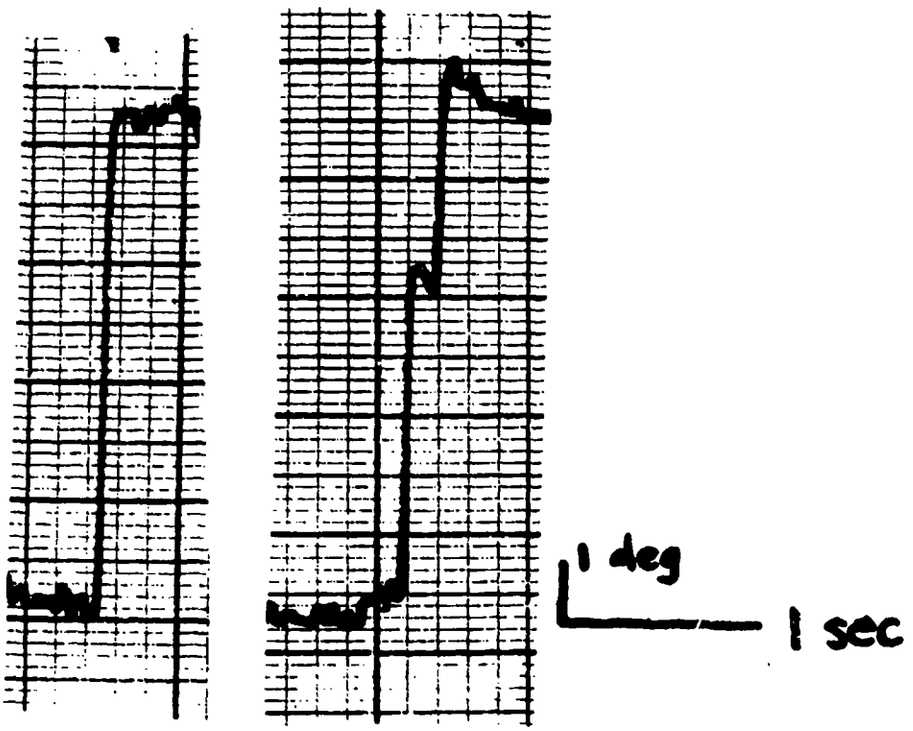

Fig. 14. Eye-movement records in response to the same change in target-position made by the same subject in the placebo condition (left) and under Valium. The placebo record shows no appreciable fixation-error or time required to stabilize the new fixation. The record under Valium (right) shows a pause little more than half way to the new fixation position followed by an overshoot and a slow return to a stabilized fixation position.

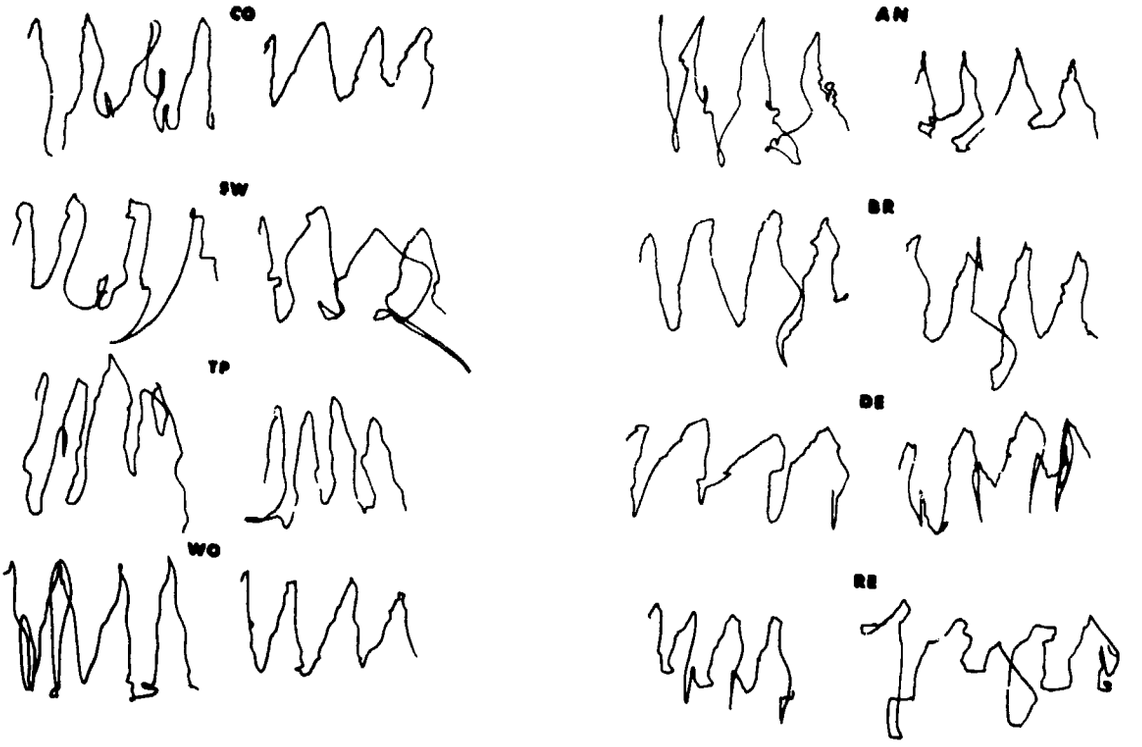

Fig. 15. Eye-movements made by subjects under Aralen (left-most curve), Dexedrine (second curve from the right) and their placebo conditions.

drug, but none of the changes was statistically significant. Under both Aralen and Digoxin, however, only one subject did not show a shorter search-time. Mean fixation-duration also decreased under Digoxin and Dexedrine; the latter change was nearly significant ($t = 2.23$, $p < .07$).

Discussion

There was a reliable increase in the magnitude of fixation-drift as the subjects attempted to maintain fixation on a stationary point under the influence of Benadryl. Errors in making a saccade from one fixation point to another also increased reliably, and there was an appreciable increase in the time taken to stabilize the new fixation. Benadryl is reported to be the most effective antihistamine in producing drowsiness, and these results may have been the result of increased drowsiness.

Valium also produced a reliable increase in the time needed to stabilize a new fixation. Our measure conforms in principle with the findings of Gentles and Llewellyn Thomas (1971) that Valium decreases the velocity of saccades. Interestingly, the amount of fixation drift and saccade error did not appreciably increase. Also of interest is the fact that only Dexedrine produced a shorter time to stabilize a new fixation.

There were no statistically significant changes in the dial-searching

experiment, although under both Aralen and Digoxin, all but one subject showed a shorter search-time to locate the target-dial.

STEREOACUITY

There appear to be virtually no studies of the effects of drugs on stereoacuity. Miller and Uhr (1960) reported that Dexedrine, in "double the normal dose" had no effect on the results of an Ortho-Rater test which includes a measure of stereoacuity.

Since it is reported that some drugs have such side-effects as diplopia, we have also tested stereoacuity. This should give some indication of any difficulties in fixating, aligning the two eyes, or fusing the two images. It should be noted, however, that some investigators have found that stereoacuity is sometimes unaffected when presumably closely related visual processes are disturbed (Wist et al, 1967; Luria, 1971; Ogle, 1953).

Method

Stereoacuity was measured with a three-rod Howard Dolman apparatus. The three vertical rods stood in a box with a 40 x 50 cm dark gray front in the center of which was a 13 x 36 cm window. The two outer rods were fixed in position in a line parallel to the front of the box. The middle rod was movable. The rods were 1.57 cm thick, positioned at 7.6 cm intervals, painted flat black, and seen against a white background. The subject sat with his head in a chin-rest at a distance of 6 m from the fixed rods. At that distance, the face and window of the apparatus subtended 3.8 x 4.7 deg and 1.2 x 3.5 deg, respectively. There was no overhead illumination in the room; the white background in the apparatus was illuminated to a relatively low level of 4 ft-L.

Thresholds were measured with the method of constant stimuli. The middle rod was set at various positions randomly and the subject required to report whether it was closer or farther than the two outer rods.

Results

The mean localization error and the mean variability of the setting (η_σ), both in seconds of arc, are given for each group in Table XIX for both the drug and placebo conditions. There were no significant changes in the mean localization error. There was a statistically significant improvement in the precision of the localization setting under Dexedrine, according to the Wilcoxon matched-pairs signed ranks test (Siegel, 1956).

Table XIX. Localization errors and variability of equidistant localization-settings (η_σ) in seconds of arc under the various drug and placebo conditions

	Localization-error		Variability	
	Drug	Placebo	Drug	Placebo
Aralen	2.95	2.85	10.25	6.73
Benadryl	3.04	2.48	5.71	4.34
Dexedrine	4.37	3.50	7.86	9.75*
Digoxin	2.03	2.40	8.07	6.67
Valium	4.05	1.85	4.12	4.82

* $p < .05$

Discussion

Although there was no significant change in the magnitude of the localization errors under the various drugs, the precision of the localization settings improved for all six subjects under Dexedrine. It is not clear why this occurred. The explanation which immediately comes to mind is that the subjects were more alert and better able to attend to their task. This improved the precision of their performance without actually improving their stereoacuity, i.e., their error of localization. As noted above, however, Tecce and Cole (1974) have reported that Dexedrine does not have the same effect on everyone. They found that 10 mg of the drug appeared to have a depressant effect on 13 of 20 adults whom they tested. And indeed at least one of our subjects complained of drowsiness after taking the drug.

The possibility that changes in stereoacuity were related to the changes in pupil size produced by the drugs (Table III) was investigated. It is widely held that the main purpose of the changes in pupil size is not so much to control the amount of light entering the eye as it is to produce the optimal depth of focus and maximize resolution acuity (Campbell and Gregory, 1960; Campbell and Green, 1965). The correlations with variability of the settings, however, were inconsistent and no correlations were found with localization error itself.

SUMMARY

The effects of drugs on the various visual tests are summarized below. It is of considerable interest that a single therapeutic dose of these widely used drugs was enough to produce a number of significant changes in basic visual processes.

Pupil Size. Digoxin significantly increased the range of the pupillary response, primarily by increasing the magnitude of dilation in dim light. Dexedrine and Benadryl also tended to increase the dilation of the pupil, the former in bright light and the latter in dim light; the result was a mean decrease in the range of response for these drugs.

Intraocular pressure was not affected. The fundus was also not appreciably changed, insofar as could be determined from its appearance and from measurements of the diameters of the blood vessels.

Color discrimination, as measured by the total error-score of the 100-Hue test, was not significantly changed by any drug. Every drug except Benadryl resulted in a mean increase in errors, but only the increase produced by Dexedrine approached significance. Aralen tended to improve the discrimination of the blues, and Dexedrine resulted in an increase in errors in the purples for every subject. Time scores were significantly affected. Dexedrine resulted in a significant decrease in the time taken to complete the test; on the other hand, five of the six subjects took longer under Benadryl.

The mixtures made on the Hecht-Shlaer anomaloscope remained within normal limits. There were no changes on the Pseudo-Isochromatic plates.

There were few changes on the color-memory test, although more saturated chips tended to be chosen under Aralen and less saturated chips tended to be chosen under Benadryl.

The Flight of colors. The duration of of this train of after-images was reliably increased by Valium. Valium was also the only drug which produced an increase in the number of green responses and a decrease in the number of red responses during the course of this phenomenon. A temporal analysis revealed a number of systematic patterns of changes in the various colors reported.

Benham's top. The subjective colors produced by this disk were not significantly altered by the drugs, although Dexedrine, Digoxin, and Valium produced twice as many hue shifts toward longer than shorter wavelengths.

Electrical activity of the brain. Benadryl and Digoxin produced significant reductions in the amplitude of the alpha component of the EEG.

Dexedrine reduced the latency of the VERs to both colored and patterned stimuli and increased the amplitude of the VERs to rapid stimulation. Aralen produced a significant decrease in the amplitude of the VERs to rapid stimulation and tended to decrease the amplitude to patterned stimuli.

Eye-movements. Benadryl and Valium increased the time needed to stabilize a new fixation. Benadryl increased the amount of drift when the subjects were fixating a stationary point and also increased the error of saccades.

Stereoacuity. Dexedrine significantly decreased the variability of the localization setting, but no drug significantly affected the magnitude of the localization error.

* * * *

We may now summarize the effects of the various tests of each drug.

Aralen produced no significant changes on any of the tests. Five of the six subjects found the target-dials in the second eye-movement experiment more quickly under Aralen. Five of the six subjects had VERs of smaller amplitude to the patterned stimuli under the drug.

Benadryl significantly reduced the amplitude of the alpha in the EEG and tended to increase the amplitude of the VERs in response to rapid flash rates. It significantly increased the magnitude of fixation drift when the subjects were fixating a stationary stimulus, increased the errors of saccades and the time taken to stabilize a new fixation. It tended to increase pupil diameter and decrease the magnitude of the range of pupil-response.

Dexedrine significantly improved the precision of the stereoacuity localization settings and decreased the amount of time taken to complete the 100-Hue test. It also led to an increase in the number of errors on that test. Dexedrine reduced the latency of the VERs and increased the amplitude of the VERs to rapid flash rates.

Digoxin significantly increased the magnitude of pupil dilation.

Valium significantly increased the duration of the flight of colors and the time needed to stabilize a new fixation. It was the only drug which resulted in a decrease in the number of red responses and an increase in the number of green responses during the flight of colors.

These changes are tabulated in Table XX.

PRACTICAL IMPLICATIONS

Benadryl significantly increased saccadic errors, the time needed to stabilize a new fixation, and the amount of drift when fixating a stationary stimulus. These findings suggest that any extended visual task would be degraded eventually. It is not certain whether or not these results stem from the tendency of this drug to produce drowsiness. In any event, even if it is no more than this, measurable effects result. Benadryl also tended to increase pupil diameter, which suggests that it will degrade acuity.

Dexedrine, as might be expected, decreased the time taken to complete the color discrimination test, but it should be noted that it also tended to increase the errors. This suggests that while

Table XX. Major effects of the present drugs on vision

Aralen	Tended to reduce search time for target-dials Tended to reduce amplitude of VERs to patterned stimuli
Benadryl	Tended to increase pupil diameter and decrease light reflex Resulted in mean improvement of color discrimination Increased errors of saccades, time to stabilize a new fixation, and amount of drift when fixating stationary stimulus
Dexedrine	Improved precision of stereoacuity Decreased time to take the 100-Hue test, but tended to increase errors Reduced latency of VERs and increased the amplitude of VERs to rapid stimulation
Digoxin	Increased pupil dilation
Valium	Extended duration of flight of colors Increased time needed to stabilize a new fixation

less demanding tasks may benefit from the increased speed, those requiring fine discrimination may suffer.

Digoxin degraded the precision of stereoacuity which could interfere with a variety of tasks.

Valium, a minor tranquilizer, increased the time to stabilize a new fixation. More interestingly, it extended the duration of the flight of colors. Aside from perhaps being an indication of the slowing down of the functioning of the nervous system, it suggests that after-images in general will be longer lasting. This may be of importance in those situations in which recovery from flash blindness is critical. Considerable effort has recently gone into determining how quickly subjects can overcome the effects of exposure to unexpected flashes, such as explosions.

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13. ABSTRACT

One therapeutic dose of five widely-used medicinal drugs (Aralen, Benadryl, Dexedrine, Digoxin, and Valium) was administered to 36 subjects. Measurements were made of the effects of the drugs on pupil size, intraocular pressure and the fundus, various aspects of color vision, the electrical activity of the brain, eye-movements and stereoacuity. A number of significant changes were observed despite the small size of the dosage and the number of subjects. The practical implications of the findings are discussed, as well as the value of visual psychophysical tests of pharmacological intoxication.

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